Synthesis of Rocaglamide Natural Products *via* Photochemical Generation of Oxidopyrylium Species

Related Applications

This application claims priority to Provisional Application No. 60/555,448, filed on March 23, 2004 and entitled "Synthesis of the Aglain Skeleton by Photogeneration and Dipolar Cycloaddition of Oxidopyryliums Derived from 3-Hydroxyflavones", and Provisional Application No. 60/612,009 filed on September 22, 2004 and entitled "Synthesis of Rocaglamide Natural Products via Photochemical Generation of Oxidopyrylium Species". Each of these provisional patent applications is incorporated herein by reference in its entirety.

Background of the Invention

The plant genus *Aglaia* native of the tropical rain forests of Indonesia and Malaysia is the source of a unique group of densely functionalized natural products presented on Figure 1 (P. Proksch *et al.*, Curr. Org. Chem., 2001, 5: 923-938). The rocaglamides, including the parent molecule (compound **1**; M.L. King *et al.*, J. Chem. Soc., Chem. Commun., 1982, 1150-1151) and the recently isolated dioxanyloxy-modified derivative silvestrol (compound **2**; B.Y. Hwang *et al.*, J. Org. Chem., 2004, 69: 3350-3358), possess a cyclopenta[*b*]tetrahydrobenzofuran ring system (presented in red on Fig. 1). The structurally related aglains (*e.g.*, compounds **3** and **4**), which contain a cyclopenta[*bc*]benzopyran structure (presented in blue on Fig. 1), have also been isolated from *Aglaia* (V. Dumontet *et al.*, Tetrahedron, 1996, 52: 6931-6942). The forbaglins (*e.g.*, compound **5**) are benzo[*b*]oxepines (in green on Fig. 1) derived from formal oxidative cleavage of the aglain core.

The rocaglamides have been shown to exhibit potent anticancer (M.L. King *et al.*, J. Chem. Soc., Chem. Commun., 1982, 1150-1151) and antileukemic activity (S.K. Lee *et al.*, Chem. Biol. Interact., 1998, 115: 215-228), as well as NF-κB inhibitory activity at nanomolar concentrations in human T cells (B. Baumann *et al.*, J. Biol. Chem., 2002, 277: 44791-44800). The rocaglate silvestrol **2** displays

cytotoxic activity against human cancer cells comparable to the anticancer drug Taxol (B.Y. Hwang *et al.*, J. Org. Chem., 2004, 69: 3350-3358).

As proposed by Proksch (P. Proksch *et al.*, Curr. Org. Chem., 2001, 5: 923-938) and Bacher (M. Bacher *et al.*, Phytochemistry, 1999, 52: 253-263), and as shown on Figure 2, the rocaglamides may be biosynthetically derived from reaction of trimethoxy-substituted 3-hydroxyflavone with cinnamide derivatives to afford the aglain core followed by skeletal rearrangement.

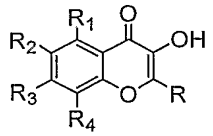
Although the rocaglamides have been the subject of a number of synthetic investigations (see, for example, G.A. Kraus and J.O. Sy, J. Org. Chem., 1989, 54: 77-83; B. Trost *et al.*, J. Am. Chem. Soc., 1990, 112: 9022-9024), including a biomimetic approach involving a [2+2] photocycloaddition (H.C. Hailes *et al.*, Tetrahedron Lett., 1993, 34: 5313-5316), syntheses of the related aglain (V. Dumontet *et al.*, Tetrahedron, 1996, 52: 6931-6942), aglaforbesin (V. Dumontet *et al.*, Tetrahedron, 1996, 52: 6931-6942), or forbaglins have not been reported. Moreover, a unified synthetic approach to these molecules based on biosynthetic considerations still remains to be developed.

Summary of the Invention

The present invention provides new methods for the synthesis of natural products. In particular, the invention encompasses novel strategies for the biomimetic preparation of compounds in the rocaglamide/aglain/forbaglin family.

More specifically, one aspect of the present invention relates to the use of a photochemically generated oxidopyrylium species as an intermediate in a chemical reaction. In certain preferred embodiments, the photochemical reaction leading to the formation of the oxidopyrylium species comprises an excited state intramolecular proton transfer.

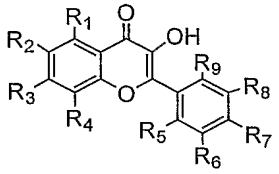
For example, the oxidopyrylium species may be produced by photochemical irradiation of a 3-hydroxychromone derivative (**I**) with the following chemical structure:



(I)

wherein R_1, R_2, R_3, R_4 and R are identical or different and selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, thioalkyl, thioaryl, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-NO_2$, -CN, $-CF_3$, $-CH_2CF_3$, $-CHCl_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-OC(=O)N(R_x)_2$, $-OC(=O)R_x$, $-OCO_2R_x$, $-S(O)R_x$, $-S(O)_2R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-N(R_x)S(O)_2R_x$, and $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl.

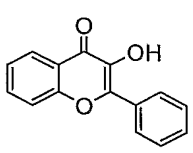
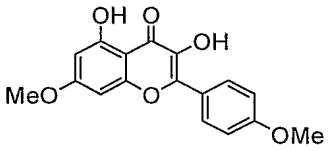
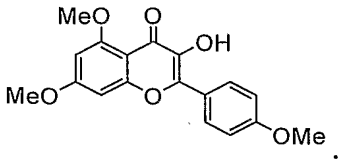
In particular, the oxidopyrylium species may be produced by photochemical irradiation of a 3-hydroxyflavone derivative (**II**) with the following chemical structure:



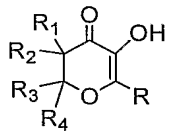
(II)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are identical or different and selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, thioalkyl, thioaryl, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-NO_2$, –CN, $-CF_3$, $-CH_2CF_3$, $-CHCl_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-OC(=O)N(R_x)_2$, $-OC(=O)R_x$, $-OCO_2R_x$, $-S(O)R_x$, $-S(O)_2R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-N(R_x)S(O)_2R_x$, and $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen,

aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl. In certain preferred embodiments, the 3-hydroxyflavone derivative has one of the following chemical structures:

Alternatively, the oxidopyrylium species may be produced by photochemical irradiation of a 5-hydroxy-2,3-dihydro-pyran-4-one derivative (**III**) with the following chemical structure:



(III)

wherein R_1, R_2, R_3, R_4 and R are identical or different and selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, thioalkyl, thioaryl, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-NO_2$, -CN, $-CF_3$, $-CH_2CF_3$, $-CHCl_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-OC(=O)N(R_x)_2$, $-OC(=O)R_x$, $-OCO_2R_x$, $-S(O)R_x$, $-S(O)_2R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-N(R_x)S(O)_2R_x$, and $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl.

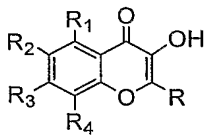
In certain embodiments, the photochemically generated oxidopyrylium species is used as an intermediate in a cycloaddition, for example a 1,3-dipolar cycloaddition, leading to the formation of an adduct.

Another aspect of the present invention relates to a method comprising steps of: photochemically generating an oxidopyrylium species; and reacting the oxidopyrylium species thus obtained with a dipolarophile. In certain preferred

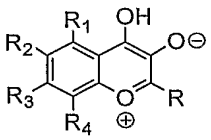
embodiments, the oxidopyrylium species is produced by photoinduced excited state intramolecular proton transfer of a 3-hydroxychromone derivative of chemical structure (**I**), or a 3-hydroxyflavone derivative of chemical structure (**II**) or a 5-hydroxy-2,3-dihydro-pyran-4-one derivative of chemical structure (**III**), as described above.

In certain embodiments, the reaction between the oxidopyrylium species and the dipolarophile (*e.g.*, a cinnamate derivative) comprises a cycloaddition, (*e.g.*, a 1,3-dipolar cycloaddition), and results in the formation of an adduct. Preferably, the adduct comprises an aglain core structure. In other embodiments, the inventive method further comprises converting the adduct formed. For example, when the adduct formed comprises an aglain core structure, converting the adduct may result in the formation of a ring system selected from the group consisting of an aglain ring system, a rocaglamide ring system, and a forbaglin ring system.

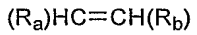
In another aspect, the present invention provides a method for preparing a compound containing an aglain core structure, said method comprising steps of: producing an oxidopyrylium species ($\mathbf{I_T}$) by photoinduced excited state intramolecular proton transfer of a 3-hydroxychromone derivative (**I**); and reacting the oxidopyrylium species with a dipolarophile (**IV**) to obtain the aglain core-containing compound (**V**). Compounds (**I**), ($\mathbf{I_T}$), (**IV**), and (**V**) have the following chemical structures:



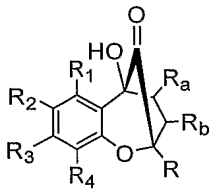
(**I**)



($\mathbf{I_T}$)



(**IV**)

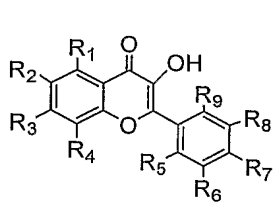


(**V**)

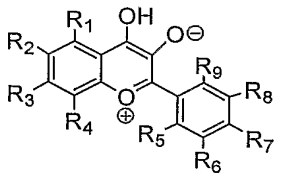
wherein R_1, R_2, R_3, R_4, R, R_a and R_b are identical or different and selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, thioalkyl, thioaryl, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-NO_2$, -CN, $-CF_3$, $-CH_2CF_3$, $-CHC1_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$,

$-OC(=O)N(R_x)_2$, $-OC(=O)R_x$, $-OCO_2R_x$, $-S(O)R_x$, $-S(O)_2R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-N(R_x)S(O)_2R_x$, and $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl.

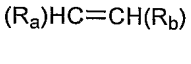
Alternatively, the method for preparing a compound containing an aglain core structure may comprising steps of: producing an oxidopyrylium species ($\mathbf{II_T}$) by photoinduced excited state intramolecular proton transfer of a 3-hydroxyflavone derivative (**II**); and reacting the oxidopyrylium species with a dipolarophile (**IV**) to obtain the aglain core-containing compound (**V'**). Compounds (**II**), ($\mathbf{II_T}$), (**IV**), and (**V'**) have the following chemical structures:



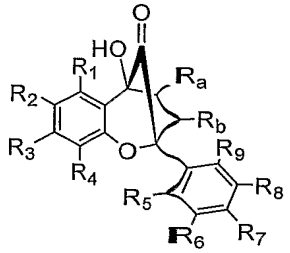
(**II**)



($\mathbf{II_T}$)



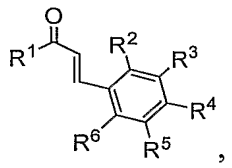
(**IV**)



(**V'**)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_a and R_b are identical or different and selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, thioalkyl, thioaryl, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-NO_2$, -CN, $-CF_3$, $-CH_2CF_3$, $-CHCl_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-OC(=O)N(R_x)_2$, $-OC(=O)R_x$, $-OCO_2R_x$, $-S(O)R_x$, $-S(O)_2R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-N(R_x)S(O)_2R_x$, and $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl.

In certain preferred embodiments of these methods, the dipolarophile (**IV**) is a cinnamate derivative with the following chemical structure:



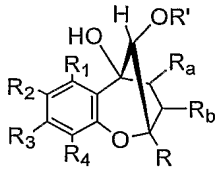
wherein R^1 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, and a protecting group; and

wherein R^2, R^3, R^4, R^5, and R^6 are identical or different and selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, thioalkyl, thioaryl, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-NO_2$, -CN, $-CF_3$, $-CH_2CF_3$, $-CHCl_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-OC(=O)N(R_x)_2$, $-OC(=O)R_x$, $-OCO_2R_x$, $-S(O)R_x$, $-S(O)_2R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-N(R_x)S(O)_2R_x$, and $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl.

In certain embodiments, the inventive methods further comprise converting the compound with an aglain core structure obtained. For example, the aglain core-containing compound may be converted into a compound with a ring system selected from the group consisting of an aglain ring system, a rocaglamide ring system, and a forbaglin ring system. Conversion into a compound with an aglain ring system may involve a reduction. Conversion into a compound with a rocaglamide ring system may comprise an α-ketol (acyloin) rearrangement (preferably under basic conditions), and optionally a hydroxyl-directed reduction. Conversion into a compound with a forbaglin ring system may comprise an oxidative cleavage.

In another aspect, the present invention relates to a method for preparing an aglain derivative, the method comprising steps of: producing an oxidopyrylium

species ($\mathbf{I_T}$) by photoinduced excited state intramolecular proton transfer of a 3-hydroxychromone derivative (**I**); reacting the oxidopyrylium species with a dipolarophile (**IV**) to obtain a compound with an aglain core structure (**V**); and converting the compound with the aglain core structure into an aglain derivative (**VI**). Compounds (**I**), ($\mathbf{I_T}$), (**IV**), and (**V**) are as described above and compound (**VI**) has the following chemical structure:

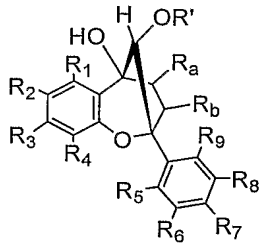


(VI)

wherein R_1, R_2, R_3, R_4, R, R_a and R_b are identical or different and selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, thioalkyl, thioaryl, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-NO_2$, -CN, $-CF_3$, $-CH_2CF_3$, $-CHCl_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-OC(=O)N(R_x)_2$, $-OC(=O)R_x$, $-OCO_2R_x$, $-S(O)R_x$, $-S(O)_2R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-N(R_x)S(O)_2R_x$, and $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl; and

wherein R' is selected from the group consisting of hydrogen, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-S(O)R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, and $-N(R_x)S(O)_2R_x$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl.

Alternatively, the method for preparing an aglain derivative comprises steps of: producing an oxidopyrylium species ($\mathbf{II_T}$) by photoinduced excited state intramolecular proton transfer of a 3-hydroxyflavone derivative (**II**); reacting the oxidopyrylium species with a dipolarophile (**IV**) to obtain a compound with an aglain core structure (**V'**); and converting the compound with an aglain core structure into an aglain derivative (**VI'**). Compounds (**II**), ($\mathbf{II_T}$), (**IV**), and (**V'**) are as described above and compound (**VI'**) has the following chemical structure:



(VI')

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_a and R_b are identical or different and selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, thioalkyl, thioaryl, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-NO_2$, $-CN$, $-CF_3$, $-CH_2CF_3$, $-CHCl_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-OC(=O)N(R_x)_2$, $-OC(=O)R_x$, $-OCO_2R_x$, $-S(O)R_x$, $-S(O)_2R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-N(R_x)S(O)_2R_x$, and $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl; and

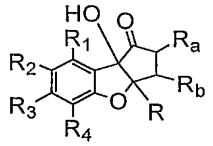
wherein R' is selected from the group consisting of hydrogen, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-S(O)R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, and $-N(R_x)S(O)_2R_x$, wherein each occurrence of R_x is independently selected from the

group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl.

In certain embodiments of these methods, the dipolarophile (**IV**) is a cinnamate derivative as described above.

In certain preferred embodiments, converting the compound with an aglain core structure into an aglain derivative involves a reduction, for example carried out in the presence of $NaBH_4$, $Me_4NBH(OAc)_3$ or another suitable reducing agent. Alternatively, addition of nucleophiles, *e.g.*, Grignard or alkylithium reagents, may be performed to convert the aglain core-containing compound into an aglain derivative.

In another aspect, the present invention relates to a method for preparing a rocaglamide derivative, the method comprising steps of: producing an oxidopyrylium species ($\mathbf{I_T}$) by photoinduced excited state intramolecular proton transfer of a 3 hydroxychromone derivative (**I**); reacting the oxidopyrylium species obtained with a dipolarophile (**IV**) to obtain a compound with an aglain core structure (**V**); and converting the compound with an aglain core structure into a rocaglamide derivative (**VII**). Compounds (**I**), ($\mathbf{I_T}$), (**IV**), and (**V**) are as described above and (**VII**) has the following chemical structures:

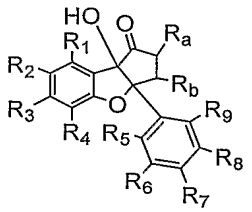


(VII)

wherein R_1, R_2, R_3, R_4, R, R_a and R_b are identical or different and selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, thioalkyl, thioaryl, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-NO_2$, -CN, $-CF_3$, $-CH_2CF_3$, $-CHC1_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-OC(=O)N(R_x)_2$, $-OC(=O)R_x$, $-OCO_2R_x$, $-S(O)R_x$, $-S(O)_2R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-N(R_x)S(O)_2R_x$, and $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen,

aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl.

Alternatively, the method for preparing a rocaglamide derivative comprises steps of: producing an oxidopyrylium species ($\mathbf{II_T}$) by photoinduced excited state intramolecular proton transfer of a 3-hydroxyflavone derivative (**II**); reacting the oxidopyrylium species obtained with a dipolarophile (**IV**) to obtain a compound with an aglain core structure (**V'**); and converting the compound with an aglain core structure into a rocaglamide derivative (**VII'**). Compounds (**II**), ($\mathbf{II_T}$), (**IV**), and (**V'**) are as described above and (**VII'**) has the following chemical structures:



(VII')

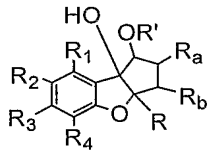
wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_a and R_b are identical or different and selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, thioalkyl, thioaryl, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-NO_2$, -CN, $-CF_3$, $-CH_2CF_3$, $CHCl_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-OC(=O)N(R_x)_2$, $-OC(=O)R_x$, $-OCO_2R_x$, $-S(O)R_x$, $-S(O)_2R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-N(R_x)S(O)_2R_x$, and $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl.

In certain embodiments of these methods, the dipolarophile (**IV**) is a cinnamate derivative as described above.

In certain preferred embodiments, converting the compound with an aglain core structure into a rocaglamide derivative comprises an α-ketol (acyloin)

rearrangement and optionally a hydroxyl-directed reduction. Preferably, the α-ketol rearrangement is carried out under basic conditions.

Another aspect of the present invention relates to a method for preparing a rocaglamide derivative, the method comprising steps of: producing an oxidopyrylium species (I_T) by photoinduced excited state intramolecular proton transfer of a 3-hydroxychromone derivative (**I**); reacting the oxidopyrylium species obtained with a dipolarophile (**IV**) to obtain a compound with an aglain core structure (**V**); and converting the compound with an aglain core structure into a rocaglamide derivative (**VIII**). Compounds (**I**), (I_T), (**IV**), and (**V**) are as described and compound (**VIII**) has the following chemical structures:



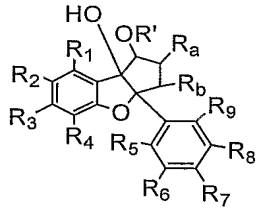
(VIII)

wherein R_1, R_2, R_3, R_4, R, R_a and R_b are identical or different and selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, thioalkyl, thioaryl, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-NO_2$, -CN, $-CF_3$, $-CH_2CF_3$, $-CHCl_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-OC(=O)N(R_x)_2$, $-OC(=O)R_x$, $-OCO_2R_x$, $-S(O)R_x$, $-S(O)_2R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-N(R_x)S(O)_2R_x$, and $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl; and

wherein R' is selected from the group consisting of hydrogen, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-S(O)R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, and

$-N(R_x)S(O)_2R_x$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl.

Alternatively, the method for preparing a rocaglamide derivative comprises steps of: producing an oxidopyrylium species ($\mathbf{II_T}$) by photoinduced excited state intramolecular proton transfer of a 3-hydroxyflavone derivative (**II**); reacting the oxidopyrylium species obtained with a dipolarophile (**IV**) to obtain a compound with an aglain core structure (**V'**); and converting the compound with an aglain core structure into a rocaglamide derivative (**VIII'**). Compounds (**II**), ($\mathbf{II_T}$), (**IV**), and (**V'**) are as described above and compound (**VIII'**) has the following chemical structures:



(VIII')

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_a and R_b are identical or different and selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, thioalkyl, thioaryl, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-NO_2$, -CN, $-CF_3$, $-CH_2CF_3$, $-CHCl_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-OC(=O)N(R_x)_2$, $-OC(=O)R_x$, $-OCO_2R_x$, $-S(O)R_x$, $-S(O)_2R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-N(R_x)S(O)_2R_x$, and $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl; and

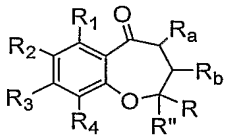
wherein R' is selected from the group consisting of hydrogen, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino

aryl, a protecting group, -CH_2OH, -CH_2CH_2OH, -$CH_2SO_2CH_3$, -$C(=O)R_x$, -$CO_2(R_x)$, -$C(=O)N(R_x)_2$, -$S(O)R_x$, -$NR_x(CO)R_x$, -$N(R_x)CO_2R_x$, -$N(R_x)C(=O)N(R_x)_2$, and -$N(R_x)S(O)_2R_x$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl.

In certain embodiments of these methods, the dipolarophile (**IV**) is a cinnamate derivative as described above.

In certain preferred embodiments, converting the compound with an aglain core structure into a rocaglamide derivative comprises an α-ketol (acyloin) rearrangement and optionally a hydroxyl-directed reduction. Preferably, the α-ketol rearrangement is carried out under basic conditions.

In another aspect, the present invention relates to a method for preparing a forbaglin derivative, the method comprising steps of: producing an oxidopyrylium species ($\mathbf{I_T}$) by photoinduced excited state intramolecular proton transfer of a 3-hydroxychromone derivative (**I**); reacting the oxidopyrylium species obtained with a dipolarophile (**IV**) to obtain a compound with an aglain core structure (**V**); and converting the compound with an aglain core into a forbaglin derivative (**IX**). Compounds (**I**), ($\mathbf{I_T}$), (**IV**), and (**V**) are as described above and compound (**IX**) has the following chemical structures:

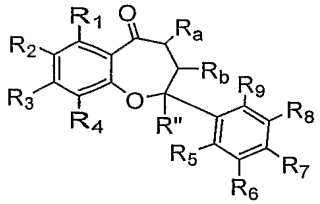


(IX)

wherein R_1, R_2, R_3, R_4, R, R", R_a and R_b are identical or different and selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, thioalkyl, thioaryl, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, -NO_2, -CN, -CF_3, -CH_2CF_3, -$CHC1_2$, -CH_2OH, -CH_2CH_2OH, -$CH_2SO_2CH_3$, -$C(=O)R_x$, -$CO_2(R_x)$, -$C(=O)N(R_x)_2$, -$OC(=O)N(R_x)_2$, -$OC(=O)R_x$, -OCO_2R_x, -$S(O)R_x$, -$S(O)_2R_x$, -$NR_x(CO)R_x$,

$-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-N(R_x)S(O)_2R_x$, and $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl.

Alternatively, the method for preparing a forbaglin derivative comprises steps of: producing an oxidopyrylium species ($\mathbf{II_T}$) by photoinduced excited state intramolecular proton transfer of a 3-hydroxyflavone derivative (**II**); reacting the oxidopyrylium species obtained with a dipolarophile (**IV**) to obtain a compound with an aglain core structure (**V'**); and converting the compound with an aglain core into a forbaglin derivative (**IX'**). Compounds (**II**), ($\mathbf{II_T}$), (**IV**), and (**V'**) are as described above and compound (**IX'**) has the following chemical structures:



(**IX'**)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R", R_a and R_b are identical or different and selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, thioalkyl, thioaryl, acyl, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylamino, amino alkyl, arylamino, amino aryl, a protecting group, $-NO_2$, -CN, $-CF_3$, $-CH_2CF_3$, $-CHCl_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-OC(=O)N(R_x)_2$, $-OC(=O)R_x$, $-OCO_2R_x$, $-S(O)R_x$, $-S(O)_2R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-N(R_x)S(O)_2R_x$, and $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x is independently selected from the group consisting of hydrogen, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, and heteroaryl.

In certain embodiments of these methods, the dipolarophile (**IV**) is a cinnamate derivative as described above.

In certain preferred embodiments, converting the compound with an aglain core structure into a forbaglin derivative comprises an oxidative cleavage, for example, an oxidative cleavage carried out in the presence of $Pb(OAc)_4$.

Another aspect of the present invention relates to aglain core containing compounds (V) and (V'), aglain derivatives (VI) and (VI'), rocaglamide derivatives (VII), (VII'), (VIII) and (VIII'), and forbaglin derivatives (IX) and (IX') prepared by the methods disclosed herein.

Another aspect of the present invention relates to the use of these compounds and derivatives for the manufacture of medicaments for use in the treatment of disease states including cancer or cancerous conditions, conditions associated with cellular hyperproliferation, and NF-κB-associated conditions.

For example, cancer and cancerous conditions that may be treated by such medicaments include leukemia, sarcoma, breast, colon, bladder, pancreatic, endometrial, head and neck, mesothelioma, myeloma, oesophagal/oral, testicular, thyroid, cervical, bone, renal, uterine, prostate, brain, lung, ovarian, skin, liver and bowel and stomach cancers, tumors and melanomas. Conditions associated with cellular hyperproliferation that can be treated using the inventive medicaments may be selected from the group consisting of atherosclerosis, restenosis, rheumatoid arthritis, osteoarthritis, inflammatory arthritis, psoriasis, periodontal disease and virally induced cellular hyperproliferation. NF-κB associated conditions that can be treated using the medicaments disclosed herein may be selected from the group consisting of immunological disorders, septic shock, transplant rejection, radiation damage, reperfusion injuries after ischemia, arteriosclerosis and neurodegenerative diseases.

Brief Description of the Drawing

FIG. 1 shows the chemical structures of Rocaglamide and related natural compounds isolated from the plant genus *Aglaia*.

FIG. 2 shows a reaction scheme proposed by Proksch and coworkers (Curr. Org. Chem., 2001, 5: 923-938) for the biosynthetic preparation of the rocaglamides.

FIG. 3 shows an embodiment of the inventive unified biomimetic approach to the synthesis of Aglains-Forbaglins-Rocaglamides.

FIG. 4 is a scheme showing the excited state intramolecular proton transfer (ESIPT) process and fluorescence emission taking place upon photoirradiation of the parent molecule, 3-hydroxyflavone.

FIG. 5 shows the reaction of photochemical [3+2] cycloaddition between 3-hydroxyflavone **13** and methyl cinnamate **14**.

FIG. 6 shows the ^{1}H-NMR (400 MHz, $CDCl_3$) (**A**) and ^{13}C-NMR (75 MHz, $CDCl_3$) (**B**) spectra recorded for compound **16**, which results from photochemical [3+2] cycloaddition between 3-hydroxyflavone **13** and methyl cinnamate **14**.

FIG. 7 shows the ^{1}H-NMR spectrum (400 MHz, CD_3CN) of a mixture of 3-hydroxyflavone **13** (1 equivalent) and methyl cinnamate **14** (5 equivalents) after 2 hours of irradiation. The chemical structure of methyl cinnamate **14** is presented in red and the chemical structure of compound **16**, the main product of the reaction, is presented in blue.

FIG. 8 shows parts (3 to 5 ppm) of expanded ^{1}H-NMR spectra (400 MHz, CD_3CN) recorded for compound **16** (**FIG. 8(A)**); and for a mixture of 3 hydroxyflavone **13** and methyl cinnamate **14** after 2 hours of irradiation (**FIG. 8(B)**).

FIG. 9 shows an example of chemical conversion of an aglain core structure to forbaglin and rocaglamide ring systems.

FIG. 10 shows the ^{1}H-NMR (400 MHz, $CDCl_3$) (**A**) and ^{13}C-NMR (75 MHz, $CDCl_3$) (**B**) spectra recorded for compound **23**.

FIG. 11 is a scheme presenting an example of synthesis of (±) methyl rocaglate from trimethoxy-substituted 3-hydroxyflavone.

FIG. 12 shows the reaction sequence used to synthesize trimethoxy-substituted 3-hydroxyflavone **24**.

FIG. 13 shows the chemical structures of compound **27**, keto isomer **27'** and enol isomer **27"**.

FIG. 14 shows the ^{1}H-NMR (400 MHz, $CDCl_3$) (**A**) and ^{13}C-NMR (75 MHz, $CDCl_3$) (**B**) spectra recorded for compound **28**.

FIG. 15 shows the ^{1}H-NMR (400 MHz, $CDCl_3$) (**A**) and ^{13}C-NMR (75 MHz, $CDCl_3$) (**B**) spectra recorded for compound **29**.

FIG. 16 shows the HMQC spectrum of synthetic *exo* methyl rocaglate **29** (500 MHz, $CHCl_3$, 25°C).

FIG. 17 shows the HMBC spectrum of synthetic *exo* methyl rocaglate **29** (500 MHz, $CHCl_3$, 25°C).

FIG. 18 shows the HMBC spectrum of synthetic *exo* methyl rocaglate **29** (500 MHz, $CHCl_3$, 25°C).

FIG. 19 shows the chemical structures of compounds **30** and **31**, obtained from chemical modifications of compounds **16** and **15**, respectively.

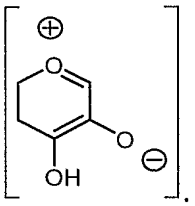
FIG. 20 shows the X-ray Crystal Structure of Compound **30**.

FIG. 21 shows the X-ray Crystal Structure of Compound **31**.

Definitions

Throughout the specification, several terms are employed that are defined in the following paragraphs.

The terms "***oxidopyrylium species***" and "***oxidopyrylium ylide species***" are used herein interchangeably. An oxidopyrylium species is a dipolar entity, *i.e.*, an electrically neutral molecule carrying a positive charge and a negative charge in one of its major canonical descriptions. In the context of the present invention, an oxidopyrylium species preferably comprises the following chemical group/motif:



Preferred oxidopyrylium species have chemical structure ($\mathbf{I_T}$) or ($\mathbf{II_T}$). In most of the inventive methods provided herein, an oxidopyrylium species is photochemically generated and used as an intermediate in a chemical reaction.

The terms "***photochemically generated***" and "***generated in a photochemical reaction***" are used herein interchangeably to characterize a chemical entity whose formation is caused/initiated by absorption of ultraviolet, visible, or infrared radiation. Similarly, a chemical process or reaction is "***photoinduced***" if it is caused/initiated by absorption of ultraviolet, visible, or infrared radiation. A wide variety of chemical processes/reactions may be photoinduced including, but not limited to, additions, cyclizations, eliminations, enolizations, rearrangements, isomerizations, oxidations, reductions, substitutions, and the like.

As used herein, the term "***intermediate***" refers to a molecular entity with a lifetime appreciably longer than a molecular vibration that is formed (directly or indirectly) from one or more reactants and reacts further to give (either directly or indirectly) the product(s) of a chemical reaction.

The term "***cycloaddition***", as used herein, refers to a chemical reaction in which two or more π-electron systems (*e.g.*, unsaturated molecules or parts of the same unsaturated molecule) combine to form a cyclic product in which there is a net reduction of the bond multiplicity. In a cycloaddition, the π electrons are used to form new σ bonds. The product of a cycloaddition is called an "***adduct***" or a "***cycloadduct***". Different types of cycloaddition are known in the art including, but not limited to, 1,3-dipolar cycloadditions and Diels-Alder reactions.

As used herein, the term "***converting***" refers to a process or reaction that is aimed at modifying a chemical compound. A variety of processes or reactions can be used to convert or modify a chemical compound including, but not limited to,

additions, eliminations, substitutions, oxidations, reductions, enolizations, rearrangements, isomerizations, and the like.

The term "***aliphatic***", as used herein, includes both saturated and unsaturated, straight chain (*i.e.*, unbranched) or branched aliphatic hydrocarbons, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, the term "aliphatic" is intended herein to include, but is not limited to, alkyl, alkenyl, or alkynyl moieties. As used herein, the term "alkyl" includes straight and branched alkyl groups. An analogous convention applies to other generic terms such as "alkenyl", "alkynyl" and the like. Furthermore, as used herein, the terms "alkyl", "alkenyl", "alkynyl" and the like encompass both substituted and unsubstituted groups. In certain embodiments, as used herein, "lower alkyl" is used to indicate those alkyl groups (substituted, unsubstituted, branched or unbranched) having 1-6 carbon atoms. "Lower alkenyl" and "lower alkynyl" respectively include corresponding 1-6 carbon moieties.

In certain embodiments, the alkyl, alkenyl and alkynyl groups employed in the invention contain 1-20; 2-20; 3-20; 4-20; 5-20; 6-20; 7-20 or 8-20 aliphatic carbon atoms. In certain other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-10; 2-10; 3-10; 4-10; 5-10; 6-10; 7-10 or 8-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-8; 2-8; 3-8; 4-8; 5-8; 6-20 or 7-8 aliphatic carbon atoms. In still other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-6; 2-6; 3-6; 4-6 or 5-6 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-4; 2-4 or 3-4 carbon atoms. Illustrative aliphatic groups thus include, but are not limited to, for example, methyl, ethyl, n-propyl, isopropyl, allyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, sec-pentyl, isopentyl, tert-pentyl, n hexyl, sec-hexyl, moieties and the like, which again, may bear one or more substituents. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-l-yl, and the like. Representative alkynyl groups include, but are not limited to, ethynyl, 2-propynyl (propargyl), 1-propynyl and the like.

The term "***alicyclic***", as used herein, refers to compounds which combine the properties of aliphatic and cyclic compounds and include, but are not limited to, monocyclic, or polycyclic aliphatic hydrocarbons and bridged cycloalkyl compounds, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, the term "alicyclic" is intended herein to include, but is not limited to, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties, which are optionally substituted with one or more functional groups. Illustrative alicyclic groups thus include, but are not limited to, for example, cyclopropyl, $-CH_2$-cyclopropyl, cyclobutyl, $-CH_2$-cyclobutyl, cyclopentyl, $-CH_2$-cyclopentyl, cyclohexyl, $-CH_2$-cyclohexyl, cyclohexenylethyl, cyclohexanylethyl, norborbyl moieties and the like, which again, may bear one or more substituents.

The term "***alkoxy***" or "***alkyloxy***", as used herein refers to a saturated (*i.e.*, O-alkyl) or unsaturated (*i.e.*, O-alkenyl and O-alkynyl) group attached to the parent molecular moiety through an oxygen atom. In certain embodiments, the alkyl group contains 1-20; 2-20; 3-20; 4-20; 5-20; 6-20; 7-20 or 8-20 aliphatic carbon atoms. In certain other embodiments, the alkyl group contains 1-10; 2-10; 3-10; 4-10; 5-10; 6-10; 7-10 or 8-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-8; 2-8; 3-8; 4-8; 5-8; 6-20 or 7-8 aliphatic carbon atoms. In still other embodiments, the alkyl group contains 1-6; 2-6; 3-6; 4-6 or 5-6 aliphatic carbon atoms. In yet other embodiments, the alkyl group contains 1-4; 2-4 or 3-4 aliphatic carbon atoms. Examples of alkoxy groups, include but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, *i*-butoxy, *sec*-butoxy, *tert*-butoxy, neopentoxy, n-hexoxy and the like.

The term "***thioalkyl***", as used herein, refers to a saturated (*i.e.*, S-alkyl) or unsaturated (*i.e.*, S-alkenyl and S-alkynyl) group attached to the parent molecular moiety through a sulfur atom. In certain embodiments, the alkyl group contains 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl group contains 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl group contains 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl group contains 1-4 aliphatic carbon atoms. Examples of

thioalkyl groups include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, and the like.

The term "***alkylamino***" refers to a group having the structure $-NHR_a$ wherein R_a is aliphatic or alicyclic, as defined herein. The term "***amino alkyl***" refers to a group having the structure NH_2R_a-, wherein R_a is aliphatic or alicyclic, as defined herein. In certain embodiments, the aliphatic or alicyclic group contains 1-20 aliphatic carbon atoms. In certain other embodiments, the aliphatic or alicyclic group contains 1-10 aliphatic carbon atoms. In still other embodiments, the aliphatic or alicyclic group contains 1-6 aliphatic carbon atoms. In yet other embodiments, the aliphatic or alicyclic group contains 1-4 aliphatic carbon atoms. In yet other embodiments, R_a is an alkyl, alkenyl, or alkynyl group containing 1-8 aliphatic carbon atoms. Examples of alkylamino groups include, but are not limited to, methylamino, ethylamino, iso-propylamino and the like.

Some examples of substituents (or functional groups) of the above-described aliphatic (and other) moieties of compounds of the invention include, but are not limited to aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylaryl, heteroalkylaryl, alkylheteroaryl, heteroalkylheteroaryl, alkoxy, aryloxy, heteroalkoxy, heteroaryloxy, alkylthio, arylthio, heteroalkylthio, heteroarylthio, F, Cl, Br, I, -OH, $-NO_2$, -CN, $-CF_3$, $-CH_2CF_3$, $-CHCl_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2NH_2$, $-CH_2SO_2CH_3$, $-C(=O)R_x$, $-CO_2(R_x)$, $-C(=O)N(R_x)_2$, $-OC(=O)R_x$, $-OCO_2R_x$, $-OC(=O)N(R_x)_2$, $-N(R_x)_2$, $-OR_x$, $-SR_x$, $-S(O)R_x$, $-S(O)_2R_x$, $-NR_x(CO)R_x$, $-N(R_x)CO_2R_x$, $-N(R_x)S(O)_2R_x$, $-N(R_x)C(=O)N(R_x)_2$, $-S(O)_2N(R_x)_2$, wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aryl, heteroaryl, alkylaryl, alkylheteroaryl, heteroalkylaryl or heteroalkylheteroaryl, wherein any of the aliphatic, alicyclic, heteroaliphatic, heterocyclic, alkylaryl, or alkylheteroaryl groups described above and herein may be substituted or unsubstituted, branched or unbranched, saturated or unsaturated, and wherein any of the aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted.

In general, the term "***aromatic moiety***" or "***aromatic***", as used herein, refers to a stable mono- or poly-cyclic, unsaturated moiety having preferably 3-14 carbon atoms, each of which may be substituted or unsubstituted. In certain embodiments, the term "aromatic moiety" refers to a planar ring having p-orbitals perpendicular to the plane of the ring at each ring atom and satisfying the Huckel rule where the number of π electrons in the ring is (4n+2) wherein n is an integer. A mono- or polycyclic, unsaturated moiety that does not satisfy one or all of these criteria for aromaticity is defined herein as "non-aromatic", and is encompassed by the term "alicyclic".

In general, the term "***heteroaromatic***", as used herein, refers to a stable mono- or polycyclic, unsaturated moiety having preferably 3-14 carbon atoms, each of which may be substituted or unsubstituted; and comprising at least one heteroatom selected from O, S and N within the ring (*i.e.*, in place of a ring carbon atom). In certain embodiments, the term "heteroaromatic moiety" refers to a planar ring comprising at least one heteroatom, having p-orbitals perpendicular to the plane of the ring at each ring atom, and satisfying the Huckel rule where the number of π electrons in the ring is (4n+2) wherein n is an integer.

It will also be appreciated that aromatic and heteroaromatic moieties, as defined herein may be attached *via* an alkyl or heteroalkyl moiety and thus also include –(alkyl)aromatic, -(heteroalkyl)aromatic, -(heteroalkyl)heteroaromatic, and -(heteroalkyl)heteroaromatic moieties. Thus, as used herein, the phrases "aromatic or heteroaromatic moieties" and "aromatic, heteroaromatic, –(alkyl)aromatic, -(heteroalkyl)aromatic, -(heteroalkyl)heteroaromatic, and –(heteroalkyl) hetero-aromatic" are interchangeable. Substituents include, but are not limited to, any of the previously mentioned substituents, *i.e.*, the substituents recited for aliphatic moieties, or for other moieties as disclosed herein, resulting in the formation of a stable compound.

The term "***aryl***", as used herein, does not differ significantly from the common meaning of the term in the art, and refers to an unsaturated cyclic moiety comprising at least one aromatic ring. In certain embodiments, the term"aryl" refers to a mono-

or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like.

The term "***heteroaryl***", as used herein, refers to a cyclic aromatic radical having from five to ten ring atoms of which one ring atom is selected from S, O and N; zero, one or two ring atoms are additional heteroatoms independently selected from S, O and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule *via* any of the ring atoms, such as, for example, pyridyl, pyrazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, and the like.

It will be appreciated that aryl and heteroaryl groups (including bicyclic aryl groups) can be unsubstituted or substituted, wherein substitution includes replacement of one or more of the hydrogen atoms thereon independently with any one or more substituents. Suitable substituents include, but are not limited to, any of the previously mentioned substituents, *i.e.*, the substituents recited for aliphatic moieties, or for other moieties as disclosed herein, resulting in the formation of a stable compound.

The term "***cycloalkyl***", as used herein, refers specifically to groups having three to seven, preferably three to ten carbon atoms. Suitable cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, which, as in the case of aliphatic, alicyclic, heteroaliphatic or heterocyclic moieties, may optionally be substituted with any of the previously mentioned substituents.

The term "***heteroaliphatic***", as used herein, refers to aliphatic moieties in which one or more carbon atoms in the main chain have been substituted with a heteroatom. Thus, a heteroaliphatic group refers to an aliphatic chain which contains one or more oxygen, sulfur, nitrogen, phosphorus or silicon atoms, *e.g.*, in place of carbon atoms. Heteroaliphatic moieties may be linear or branched, and saturated or unsaturated. In certain embodiments, heteroaliphatic moieties are substituted by independent replacement of one or more of the hydrogen atoms thereon with one or more of the previously mentioned subsituents.

The term "***heterocycloalkyl***", "***heterocycle***" or "***heterocyclic***", as used herein, refers to compounds which combine the properties of heteroaliphatic and cyclic compounds and include, but are not limited to, saturated and unsaturated mono- or polycyclic cyclic ring systems having 5-16 atoms wherein at least one ring atom is a heteroatom selected from O, S and N (wherein the nitrogen and sulfur heteroatoms may optionally be oxidized), wherein the ring systems are optionally substituted with one or more functional groups, as defined herein. In certain embodiments, the term "heterocycloalkyl", "heterocycle" or "heterocyclic" refers to a non-aromatic 5-, 6- or 7- membered ring or a polycyclic group wherein at least one ring atom is a heteroatom selected from O, S and N (wherein the nitrogen and sulfur heteroatoms may optionally be oxidized), including, but not limited to, a bi- or tri-cyclic group, comprising fused six-membered rings having between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein (i) each 5-membered ring has 0 to 2 double bonds, each 6-membered ring has 0 to 2 double bonds and each 7-membered ring has 0 to 3 double bonds, (ii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to an aryl or heteroaryl ring. Representative heterocycles include, but are not limited to, heterocycles such as furanyl, thiofuranyl, pyranyl, pyrrolyl, pyrazolyl, imidazolyl, thienyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolyl, oxazolidinyl, isooxazolyl, isoxazolidinyl, dioxazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, triazolyl, thiatriazolyl, oxatriazolyl, thiadiazolyl, oxadiazolyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, dithiazolyl, dithiazolidinyl, tetrahydrofuryl, and benzofused derivatives thereof. The term "heterocycle, or heterocycloalkyl or heterocyclic" also encompasses heterocycle, or heterocycloalkyl or heterocyclic groups that are substituted by the independent replacement of one, two or three of the hydrogen atoms thereon with any of the previously mentioned substituents. Additionally, it will be appreciated that any of the alicyclic or heterocyclic moieties described above and herein may comprise an aryl or heteroaryl moiety fused thereto.

The terms "***halo***" and "***halogen***", as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

The term "***haloalkyl***" denotes an alkyl group, as defined above, having one, two, or three halogen atoms attached thereto and is exemplified by such groups as chloromethyl, bromoethyl, trifluoromethyl, and the like.

The term "***amino***", as used herein, refers to a primary ($-NH_2$), secondary ($-NHR_x$), tertiary ($-NR_xR_y$) or quaternary ($-N^+R_xR_yR_z$) amine, where R_x, R_y and R_z are independently an aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic or heteroaromatic moiety, as defined herein. Examples of amino groups include, but are not limited to, methylamino, dimethylamino, ethylamino, diethylamino, diethylaminocarbonyl, methylethylamino, iso-propylamino, piperidino, trimethylamino, and propylamino.

The term "***acyl***", as used herein, refers to a group having the general formula $-C(=O)R_b$, where R_b is an aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic or heteroaromatic moiety, as defined herein.

As used herein, the terms "***aliphatic***", "***heteroaliphatic***", "***alkyl***", "***alkenyl***", "***alkynyl***", "***heteroalkyl***", "***heteroalkenyl***", "***heteroalkynyl***", and the like encompass substituted and unsubstituted, saturated and unsaturated, and linear and branched groups. Similarly, the terms "***alicyclic***", "***heterocyclic***", "***heterocycloalkyl***", "***heterocycle***" and the like encompass substituted and unsubstituted, and saturated and unsaturated groups. Additionally, the terms "***cycloalkyl***", "***cycloalkenyl***", "***cycloalkynyl***", "***heterocycloalkyl***", "***heterocycloalkenyl***", "***heterocycloalkynyl***", "***aromatic***", "***heteroaromatic***", "***aryl***", "***heteroaryl***" and the like encompass both substituted and unsubstituted groups.

By the term "***protecting group***", as used herein, it is meant that a particular functional moiety, *e.g.*, O, S, or N, is temporarily blocked so that a reaction can be carried out selectively at another reactive site in a multifunctional compound. In preferred embodiments, a protecting group reacts selectively in good yield to give a protected substrate that is stable to the projected reactions; the protecting group must be selectively removed in good yield by readily available, preferably nontoxic

reagents that do not attack the other functional groups; the protecting group forms an easily separable derivative (more preferably without the generation of new stereogenic centers); and the protecting group has a minimum of additional functionality to avoid further sites of reaction. Oxygen, sulfur, nitrogen and carbon protecting groups may be utilized. For example, oxygen protecting groups include, but are not limited to, methyl ethers, substituted methyl ethers (*e.g.*, MOM (methoxymethyl ether), MTM (methylthiomethyl ether), BOM (benzyloxymethyl ether), PMBM or MPM (p-methoxybenzyloxymethyl ether), to name a few), substituted ethyl ethers, substituted benzyl ethers, silyl ethers (*e.g.*, TMS (trimethylsilyl ether), TES (triethylsilylether), TIPS (triisopropylsilyl ether), TBDMS (t-butyldimethylsilyl ether), tribenzyl silyl ether, TBDPS (t-butyldiphenyl silyl ether), to name a few), esters (*e.g.*, formate, acetate, benzoate (Bz), trifluoroacetate, dichloroacetate, to name a few), carbonates, cyclic acetals and ketals. In certain other exemplary embodiments, nitrogen protecting groups are utilized. Nitrogen protecting groups include, but are not limited to, carbamates (including methyl, ethyl and substituted ethyl carbamates (*e.g.*, Troc), to name a few) amides, cyclic imide derivatives, N-Alkyl and N-Aryl amines, imine derivatives, and enamine derivatives, to name a few. It will be appreciated that the present invention is not intended to be limited to these protecting groups; rather, a variety of additional equivalent protecting groups can be readily identified using the above criteria and utilized in the present invention. Additionally, a variety of protecting groups are described in "*Protective Groups in Organic Synthesis*" T.W. Greene and P.G. Wuts (Eds.), John Wiley & Sons: New York, 1999 (3rd Ed), the entire contents of which are incorporated herein by reference.

As used herein, the term "***medicament***" refers to any substance or combination of substances that has a beneficial or therapeutic effect. In preferred embodiments of the present invention, the manufacture of a medicament comprises the use of at least one derivative of the rocaglamide/aglain/forbaglin family prepared by the methods provided herein. For example, a medicament according to the present invention may comprise one or more derivatives of the rocaglamide/aglain/forbaglin family as active ingredient(s). A medicament may further comprise one or more other active

ingredients, such as drugs or therapeutic agents known in the art or newly discovered agents whose activity is to be tested, and/or one or more pharmaceutically acceptable carriers. As used herein, the term "***pharmaceutically acceptable carrier***" refers to a carrier medium which does not interfere with the effectiveness of the biological activity of the active ingredients and which is not excessively toxic to the hosts at the concentrations at which it is administered. The term includes solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic agents, absorption delaying agents, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art (see, for example, Remington's Pharmaceutical Sciences, E.W. Martin, 18th Ed., 1990, Mack Publishing Co.: Easton, PA).

The term "***treatment***" is used herein to characterize a method or process that is aimed at (1) delaying or preventing the onset of a disease or condition; or (2) slowing down or stopping the progression, aggravation, or deterioration of the symptoms of the disease or condition; or (3) bringing about ameliorations of the symptoms of the disease or condition; or (4) curing the disease or condition. The treatment may be administered prior to the onset of the disease, for a prophylactic or preventive action. Alternatively or additionally, the treatment may be administered after initiation of the disease or condition, for a therapeutic action.

Detailed Description of Certain Preferred Embodiments

The present invention is directed to a new, unified biomimetic approach to the synthesis of rocaglamides and related aglains and forbaglins. An embodiment of this new approach is outlined in Figure 3.

More specifically, the inventive synthetic method shown in Figure 3 involves photochemical generation of an oxidopyrylium species (compound **7**) *via* excited state intramolecular proton transfer (ESIPT) of a 3-hydroxyflavone derivative **6** followed by 1,3-dipolar cycloaddition (*i.e.*, [3+2] cycloaddition) of the oxidopyrylium species to a dipolarophile, such as a cinnamate derivative. This reaction results in the formation of the adduct **8**, which contains an aglain core structure. Conversion of **8**

by oxidative cleavage yields forbaglin **9**, while reduction of the adduct **8** produces aglain **10**. Core structure **8** may alternatively be converted to hydrorocaglate **11** by α-ketol (acyloin) rearrangement; and hydroxyl-directed reduction of **11** affords rocaglate **12**.

I. Excited State Intramolecular Proton Transfer (ESIPT)

An ESIPT phenomenon involves a very fast intramolecular transfer of a proton. In some cases, this process takes place in only tens or hundreds of femtoseconds (M. Kasha, J. Chem. Soc. Faraday Trans. 2, 1986, 82: 2379-2392; B.J. Schwartz *et al.*, J. Phys. Chem., 1992, 96: 3591-3598; F. Laermer *et al.*, Chem. Phys. Lett., 1988, 148: 119-124).

Literature reports have documented excited state intramolecular proton transfer (see, for example, P.-T. Chou, J. Chin. Chem. Soc., 2001, 48: 651-682; A.D. Roschal *et al.*, J. Phys. Chem. A, 1998, 102: 5907-5914; A. Bader *et al.*, J. Phys. Chem. A, 2002, 106: 2844-2849 and references therein; A. Samanta *et al.*, J. Phys. Chem. A, 2003; 107: 6334-6339; A.P. Demchenko, J. Phys. Chem. A, 2003, 107: 4211-4216; R. Rastogi *et al.*, Spectrochem. Acta, Part A, 2001, 57: 299-308) of 3-hydroxyflavone derivatives leading to the formation of an oxidopyrylium species (J. Hendrickson and J.S. Farina, J. Org.Chem., 1980, 45: 3359-3361; P.G. Sammes *et al.*, J. Chem. Soc. Perkin Trans. I, 1983, 1261-1265; P.A. Wender *et al.*, J. Am. Chem. Soc., 1997, 119: 12976-12977; J.E. Baldwin *et al.*, Tetrahedron Lett., 2003; 44: 4543-4545).

The overall ESIPT process (shown on Figure 4 in the case of the parent molecule, 3-hydroxyflavone, 3-HF) involves generation of a putative tautomeric form of 3-HF, where the proton of the hydroxyl group at position C3 migrates to the ketone group at position C4 to give an oxidopyrylium species (tautomeric form **T**).

Although ESIPT processes of 3-HF derivatives have been reported in the literature to produce excited state species such as the oxidopyrylium, there are no reports of chemical reactions using these species. The present invention encompasses

the recognition by the Applicants that the reactivity of such oxidopyrylium species can be advantageously exploited in chemical reactions.

Accordingly, one aspect of the present invention relates to the use of photochemically generated oxidopyrylium species as intermediates in chemical reactions. Preferably, the oxidopyrylium species is photochemically generated *via* a process comprising an excited state intramolecular proton transfer.

As will be appreciated by those of ordinary skill in the art, any organic molecule which can produce an oxidopyrylium species upon photochemical excitation is suitable for use in the practice of the present invention. Particularly suitable compounds comprise a 5-hydroxy-pyran-4-one group/motif, including, but not limited to, 5-hydroxy-2,3-dihydro-pyran-4-one derivatives. 3-hydroxychromone derivatives (M. Itoh, Pure and Applied Chemistry, 1993, 65: 1629-1634; A.S. Klymchenko *et al.*, New J. Chem., 2004, 28: 687-692) and 3-hydroxyflavone derivatives. When the photochemically generated oxidopyrylium species is used in the preparation of rocaglamides and related aglains and forbaglins according to the new synthetic approach provided herein, the oxidopyrylium species is preferably generated by photochemical excitation of a 3-hydroxychromone derivative of chemical structure (**I**) or 3-hydroxyflavone derivative of chemical structure (**II**).

Methods for photochemically exciting organic molecules are known in the art. Photochemical irradiation of 3-hydroxyflavone derivatives is described in Example 1 and Example 5.

II. Cycladdition Reactivity of Oxidopyrylium Species

In preferred embodiments, the photochemically generated oxidopyrylium species is used as a reactive intermediate in a cycloaddition, such as a 1,3-dipolar cycloaddition.

Initial efforts by the Applicants toward understanding the cycloaddition reactivity of the oxidopyrylium species **T** (see Figure 4) were focused on model studies using 3-hydroxyflavone, the parent compound and simplest molecule of the 3-hydroxyflavone family.

Oxidopyrylium Species Generated from 3-Hydroxyflavone

Photoirradiation of 3-hydroxyflavone **13** in presence of the dipolarophile methyl cinnamate **14** was carried out in acetonitrile using a 450 W pressure mercury lamp (uranium filter, $\lambda > 350$ nm). After irradiation at room temperature for 2 hours, compound **13** was consumed and a mixture of products was obtained, resulting, presumably, from [3+2] cycloaddition (see Figure 5 and Example 1).

Based on spectroscopic data and X-ray analysis of a crystalline derivative (see Example 1), the major compound (56%) was confirmed to be the *endo* cycloadduct **16** in which the phenyl ring of the dipolarophile is *anti* to the oxido bridge (P.G. Sammes and L.J. Street, J. Phys. Chem., 1998, 102: 5907-5914). ^{1}H-NMR and ^{13}C-NMR spectra recorded for compound **16** are presented in Figure 6. Interestingly, an equilibrium between **16** and the benzo[*b*]cyclobutapyran-8-one **17** is observed during silica gel purification resulting from an acid-mediated ketol shift (X. Creary *et al.*, J. Org. Chem., 1985, 50: 1932-1938). The equilibrium between the two core structures was found to be controlled by temperature: heating a mixture of compounds **16** and **17** (ethyl acetate, 65°C) was observed to lead to the formation of compound **16** exclusively. Monitoring of the photocycloaddition by ^{1}H-NMR (in CD_3CN) also confirmed formation of **16** as the major product (see Fig. 7 and Fig. 8(A and B)).

Compound **15** (14%) was identified as a cyclopenta[*b*]tetrahydrobenzofuran by further conversion into a crystalline derivative. In contrast to **16**, compound **15** is derived from *exo* [3+2] cycloaddition to an aglaforbesin type ring system (see compound **4** in Figure 1) followed by acycloin rearrangement during the photoirradiation process (further experiments to support the ESIPT mechanism were conducted using 3-methoxyflavone). Irradiation (350 nm, acetonitrile, 5 equivalents of **18**, at room temperature) did not give a [3+2] cycloadduct but instead provided a product resulting from oxidative photocycloaddition (T. Matsuura and T. Takemo, Tetrahedron, 1973, 3337-3340).

***Conversion of Cycloadduct* 16**

Cycloadduct **16**, which contains an aglain core structure, was then evaluated for its ability to be converted to compounds containing rocaglamide and forbaglin ring

systems (as shown on Figure 9). Oxidative cleavage of the aglain core to the forbaglin ring system may be conducted using $Pb(OAc)_4$ (E. Baer, J. Am. Chem. Soc., 1940, 62: 1597-1606). Treatment of cycloadduct **16** with $Pb(OAc)_4$ in benzene/methanol at room temperature afforded benzo[*b*]oxepines **18:19** as a 2:1 mixture of keto-enol tautomers (85%) (see Example 2).

The aglain core structure of compound **16** may alternatively be converted to dehydrorocaglate by α-ketol (acyloin) rearrangement (L.A. Paquette and J.E. Hofferberth, Org. React., 2003, 62: 477-567; for ketol shifts in biogenesis, see, for example, M. Rentzea and E. Hecker, Tetrahedron Lett., 1982, 23: 1785-1788; and D.H.G. Crout and D.L. Rathbone, J. Chem. Soc. Chem. Commun., 1987, 290-291)

Attempted thermal acycloin rearrangement (J. Lui *et al.*, Tetrahedron, 1998, 54: 11637-11650) of compound **16** did not afford any observable ketol shift product. Acyloin rearrangements have alternatively been conducted using acidic or basic conditions or employing metal catalysis and have been used with success in a number of natural product syntheses (for K252a, see, for example, K. Tamaki *et al.*, Tetrahedron Lett., 2002, 43: 379-382; for Taxanes, see, for example, L. Paquette and J.E. Hofferberth, J. Org. Chem., 2003, 68: 2266-2275).

Treatment of cycloadduct **16** with protic or Lewis acidic conditions (BF3, Et_2O, $ZnCl_2$) resulted in decomposition of the starting material. However, treatment of cycloadduct **16** under basic conditions (2.5 equivalents of NaOMe, methanol) (X. Creary *et al.*, J. Org. Chem., 1985, 50: 1932-1938), afforded a 1:1 mixture of keto-enol tautomers **20:21** (see Example 3). The success of basic conditions for α-ketol rearrangement may be explained by the fact that such basic conditions favor the formation of the enolate of **21**, which may drive the ketol shift equilibrium (E. Piers *et al.*, Synlett., 1999, 7: 1082-1084) towards the rocaglamide core.

Further proof for this assumption was provided by treatment of cycloadduct **16** with NaH (2.1 equivalent, tetrahydrofuran, room temperature) and quenching of the reaction mixture with thionyl chloride, which led to the formation of the stable 1,3,2-dioxathiolane **22** (48 %) (M. Shipman *et al.*, Tetrahedron, 1999, 55: 108445-10850) (see Example 3).

Hydroxyl-directed reduction (B. Trost *et al.*, J. Am. Chem. Soc., 1990, 112: 9022-9024) of **20:21** afforded rocagolate **23** (95 %) (see Example 4). The ^{1}H-NMR and ^{13}C-NMR spectra of compound **23** are presented on Figure 10.

Oxidopyrylium Species Generated from Methoxy-Substituted 3-Hydroxyflavone

3-Hydroxyflavone derivatives with methoxy substitutions were then evaluated for their suitability in the synthesis of rocaglamides and related compounds. The overall synthetic scheme is presented on Figure 11 in the case of the trimethoxy-substituted 3-hydroxyflavone. Trimethoxy-substituted 3-hydroxyflavone was synthesized following a procedure adapted from a reaction sequence reported by H. Tanaka and coworkers (Tetrahedron Lett., 2000, 41: 9735-9739) as shown in Figure 12. Photoirradiation (uranium filter) of kaempferol derivative **24** and methyl cinnamate **14** (Y.-J. Lee and T.-D. Wu, J. Chin. Chem. Soc., 2001, 48: 201-206) in methanol at 0°C afforded the aglain **25** as well as benzo[*b*]cyclobutapyran-8-one **26** (33 % and 17 %, respectively) after purification on SiO_2 (see Example 5).

Conversion of Compounds 25 and 26

Basic conditions (NaOMe, methanol) were used to effect α-ketol rearrangement of compound **25** and compound **26** (see Example 6). In the case of compound **25**, the reaction led to the formation of a mixture of *endo* and *exo* cycloadducts **27**, in which the *endo* isomer was obtained as a mixture of keto-enol tautomers **27'/27"** (the chemical structures of compounds **27**, **27'** and **27"** are presented on Figure 12). In the case of compound **26**, the base-mediated reaction only gave the *endo* cycloadduct **27**.

Hydroxyl-directed reduction of keto rocaglate **27**, which is described in Example 7, afforded (±)-methyl rocaglate **28** (51%) and the corresponding *exo* stereoisomer **29** (27 %) (B. Trost *et al.*, J. Am. Chem. Soc., 1990, 112: 9022-9024). The ^{1}H-NMR and ^{13}C-NMR spectra of compounds **28** and **29** are reported in Figure 14 and Figure 15, respectively. Spectral data for synthetic compound **28** were in full agreement with those reported for natural methyl rocaglate (F. Ishibashi *et al.*, Phytochemistry, 1993, 32: 307-310) (see Example 7). Similarly, spectral data for

synthetic **29** were in full agreement with those reported for natural methyl rocaglate (G.A. Kraus and J.O. Sy, J. Org. Chem., 1989, 54: 77-83).

Methyl cinnamate was used as dipolarophile in most of the experiments reported herein. However, as will be appreciated by those skilled in the art, any dipolarophile exhibiting reactivity toward a photochemically generated oxidopyrylium species can be used in the practice of the synthetic methods disclosed herein.

III. Chemical Modifications of Aglain/Rocaglamide/Forbaglin Derivatives

As will be appreciated by those of ordinary skill in the art, initially formed aglain derivatives as well as the forbaglins and rocaglamides derived from them can be further chemically modified to obtain new derivatives of the aglain/rocaglamide/forbaglin family.

For example, chemical modifications may be performed to study structure-activity relationships with the goal of developing compounds that possess improved biological activity and that fulfill all stereoelectronic, physicochemical, pharmacokinetic, and toxicologic factors required for clinical usefulness. In such studies, molecular structure and biological activity are correlated by observing the results of systemic structural modification on defined biological endpoints. For example, comparison of the activity of structurally-related compounds may help identify positions and/or chemical motifs that play an important role in biological activity. Similarly, analysis of the effects of the stereochemistry (*i.e.*, the arrangement of atoms in space) of these chemically modified compounds on biological endpoints may help identify conformations that are favorable to the biological activity. The present invention is intended to encompass chemically modified derivatives of the aglain/rocaglamide/forbaglin family obtained by the methods disclosed herein.

Examples of such chemical modifications are described in Examples 8 and 9 in the case of compounds **16** and **15**, respectively. The chemical structures of the products of these chemical modifications (compound **30** and compound **31**, respectively) are shown on Figure 19.

IV. Uses of Aglain/Rocaglamide/Forbaglin Derivatives

As mentioned above, compounds in the rocaglamide/aglain/forbaglin family have been demonstrated to exhibit biological activity. In particular, a number of these compounds are potent natural insecticides (B.W. Nugroho *et al.*, Phytochemistry, 1997, 45: 1579-1585; B.W. Gussregen *et al.*, Phytochemistry, 1997, 44: 1455-1461; G. Brader *et al.*, J. Nat. Prod., 1998, 61: 1482-1490; J. Hiort Chaidir *et al.*, Phytochemistry, 1999, 52: 837-842; B.W. Nugrobo *et al.*, Phytochemistry, 1999, 51: 367-376).

Moreover, rocaglamide derivatives have been found to exhibit cytostatic activity in human cancer cell lines (B. Cui *et al.*, Tetrahedron, 1997, 53: 17625-17632; T.S. Wu *et al.*, J. Nat. Prod., 1997, 60: 606-608; S.K, Lee *et al.*, Chem. Biol. Interact., 1998, 115: 215-228) with effects comparable to those observed with established anticancer drugs such as vinblastine sulfate and actinomycin D (F.I. Bohnenstengel *et al.*, Z. Naturforsch. [C], 1999, 54: 55-60; F.I. Bohnenstengel *et al.*, Z. Naturforsch. [C], 1999, 54: 1075-1083). In particular, the rocaglate silvestrol **2** (see Figure 1) has been shown to display cytotoxic activity against human cancer cells comparable to the anticancer drug Taxol (B.Y. Hwang *et al.*, J. Org. Chem., 2004, 69: 3350-3358). Other studies have revealed that these compounds block cell cycle progression and induce apoptosis at nanomolar concentrations in colorectal tumor cell lines (B. Hausott *et al.*, Int. J. Cancer, 2004, 109: 933-940). Experimental results reported in this study suggest that apoptosis is induced *via* a p38-mediated stress pathway (B. Hausott *et al.*, Int. J. Cancer, 2004, 109: 933-940). Furthermore, rocaglamides have been demonstrated to block protein biosynthesis (T. Ohse *et al.*, J. Nat. Prod., 1996, 650-653) and to induce growth arrest in the G2/M phase in certain tumor cells (F.I. Bohnenstengel *et al.*, Z. Naturforsch. [C], 1999, 54: 1075-1083).

More recently, it was shown that rocaglamides represent highly potent and specific inhibitors of TNF-α (tumor necrosis factor-alpha) and PMA (porbol 12-myristate 13 acetate)-induced NF-κB (nuclear factor-kappa B) activity in different mouse and human T cell lines. The IC_{50} values observed for rocaglamide derivatives were in the nanomolar range whereas aglain derivatives proved inactive. Rocaglamide and several of its derivatives are among the strongest inhibitors of

NF-κB-induced gene activation known so far (B. Baumann *et al.*, J. Biol. Chem., 2002, 277: 44791-44800).

Agents that can suppress NF-κB activation have, in principle, the potential to prevent or delay onset or treat NF-κB-linked diseases. On activation, NF-κB induces the expression of more than 200 genes, that have been shown to suppress apoptosis, induce cellular transformation, proliferation, invasion, metastasis, chemoresistance, radioresistance, and inflammation (A. Garg and B.B. Aggarwal, Leukemia, 2002, 16: 1053-1056). The activated form of NF-κB has been found to mediate cancer (A. Garg and B.B. Aggarwal, Leukemia, 2002, 16: 1053-1056; A Lin and M. Karin, Semin. Cancer Biol., 2003, 13: 107-114; R.Z. Orlowski and A.S. Baldwin, Trends Mol. Med., 2002, 8: 385-389), atherosclerosis (G. Valen *et al.*, J. Am. Coll. Cardiol., 2001, 38: 307-314), myocardial infarction (W.K. Jones *et al.*, Cardiovasc. Toxicol., 2003, 3: 229-254), diabetes (S.E. Shoelson et al., Int. J. Obes. Relat. Metab. Disord., 2003, 27(Suppl. 3): S49-52), allergy (L. Yang *et al.*, J. Exp. Med., 1998, 188: 1739-1750; J. Das *et al.*, Nature Immunol., 2001, 2: 45-50), asthma (R. Gagliardo *et al.*, Am. J. Respir. Crit. Care Med., 2003, 168: 1190-1198), arthritis (A.K. Roshak *et al.*, Curr. Opin. Pharmacol., 2002, 2: 316-321), Crohn's disease (D.A. van Heel *et al.*, Hum. Mol. Genet., 2002, 11: 1281-1289), multiple sclerosis (C.J. Huang *et al.*, Int. J. Dev. Neurosci., 2002, 20: 289-296), Alzheimer's disease (M.P. Mattson and S. Camandola, J. Clin. Invest., 2001, 107: 247-254; B. Kaltschmidt *et al.*, Proc. Natl. Acad. Sci. USA, 1997, 94: 2642-2647), osteoporosis, psoriasis, septic shock, AIDS and other inflammatory diseases (J.R. Burke, Curr. Opin. Drug Discov. Devel., 2003, 6: 720-728; Y. Yamamoto and R.B. Gaynor, Curr. Mol., Med., 2001, 1: 287-296; Y. Yamamoto and R.B. Gaynor, J. Clin. Invest., 2001, 107: 135-142).

Interestingly, a synthetic derivative of the natural product rocaglaol was recently found to exhibit neuroprotective activity *in vitro* and in animal models of Parkinson's disease and traumatic brain injury (T. Fahrig *et al.*, Mol. Pharmacol., (Fast Forward" publications), Feb. 16, 2005). Experimental data reported in this study suggest that by inhibiting NF-κB and AP-1 (activator protein-1) signaling, this rocaglaol derivative is able to reduce tissue inflammation and neuronal cell death

resulting in significant neuroprotection in animal models of acute and chronic neurodegeneration.

Accordingly, another aspect of the present invention relates to the use of derivatives of the rocaglamide/aglain/forbaglin family for the manufacture of medicaments for use in the treatment of various disease states, including cancer and cancerous conditions, conditions associated with cellular hyperproliferation, and NF-κB-associated conditions. Preferably, the rocaglamide derivatives used in the manufacture of these medicaments are prepared by the inventive methods disclosed herein.

Cancer and cancerous conditions that can be treated using such medicaments may be selected from the group consisting of leukemia, sarcoma, breast, colon, bladder, pancreatic, endometrial, head and neck, mesothelioma, myeloma, oesophagal/oral, testicular, thyroid, cervical, bone, renal, uterine, prostate, brain, lung, ovarian, skin, liver and bowel and stomach cancers, tumors and melanomas. Conditions associated with cellular hyperproliferation that can be treated using the inventive medicaments may be selected from the group consisting of atherosclerosis, restenosis, rheumatoid arthritis, osteoarthritis, inflammatory arthritis, psoriasis, periodontal disease and virally induced cellular hyperproliferation. NF-κB associated conditions that can be treated using the medicaments disclosed herein may be selected from the group consisting of immunological disorders, septic shock, transplant rejection, radiation damage, reperfusion injuries after ischemia, arteriosclerosis and neurodegenerative diseases.

The medicaments according to the present invention may be in a liquid, aerosol or solid dosage form, and may be manufactured into any suitable formulation including, but not limited to, solutions, suspensions, micelles, emulsions, microemulsions, syrups, elixirs aerosols, ointments, gels suppositories, capsules, tablets, pills, dragees, and the like, as will be required for the appropriate route of administration.

Any suitable route of administration of the inventive medicaments is encompassed by the present invention including, but not limited to, oral, intravemous,

intraperitoneal, intramuscular, subcutaneous, inhalation, intranasal, topical, rectal or other administration route known in the art. The route of administration, formulation and dosage of the medicament will be dependent upon a variety of factors including the pathophysiological condition to be treated and the severity and/or extent of the disorder, the age, sex, weight and general health of the particular patient, the potency, bioavailability, *in vivo* half-life and severity of the side effects of the specific rocaglamide derivative(s) employed in the manufacture of the medicament, the time of administration, the duration of the treatment, drugs used in combination or coincidental with the specific rocaglamide derivative(s) employed, and similar factors well known in the art. These factors are readily determined in the course of therapy. Alternatively or additionally, the dosage to be administered can be determined from studies using animal models for the particular condition to be treated, and/or from animal or human data obtained for compounds which are known to exhibit similar pharmacological activities. A medicament may be formulated in such a way that the total dose required for each treatment is administered by multiple dose or in a single dose. In certain embodiments, the medicament is manufactured or formulated in dosage unit form. The expression "dosage unit form", as used herein, refers to a physically discrete unit of medicament appropriate for the condition/patient to be treated.

In certain embodiments, a medicament according to the present invention comprises one or more rocaglamide derivatives as active ingredients. In other embodiments, the medicament further comprises one or more other therapeutic agents. The nature of such additional therapeutic agent(s) will depend on the condition to be treated by administration of the medicament. The ability to determine combinations of compounds suitable to treat particular disorders is well within the capabilities of trained scientists or physicians. For example, a medicament according to the present invention for use in the treatment of cancer may further comprise approved chemotherapeutic drugs, including, but not limited to, alkylating drugs (mechlorethamine, chlorambucil, Cyclophosphamide, Melphalan, Ifosfamide), antimetabolites (Methotrexate), purine antagonists and pyrimidine antagonists (6-Mercaptopurine, 5-Fluorouracil, Cytarabile, Gemcitabine), spindle poisons

(Vinblastine, Vincristine, Vinorelbine, Paclitaxel), podophyllotoxins (Etoposide, Irinotecan, Topotecan), antibiotics (Doxorubicin, Bleomycin, Mitomycin), nitrosoureas (Carmustine, Lomustine), inorganic ions (Cisplatin, Carboplatin), enzymes (Asparaginase), and hormones (Tamoxifen, Leuprolide, Flutamide, and Megestrol), to name a few. For a more comprehensive discussion of updated cancer therapies see, http://www.nci.nih.gov/, a list of the FDA approved oncology drugs at http://www.fda.gov/cder/cancer/druglistframe.htm, and The Merck Manual, 7th Ed. 1999, the entire contents of which are hereby incorporated by reference.

In addition to the active ingredient(s), the medicament may further comprise one or more pharmaceutically acceptable carriers, including, but not limited to, inert diluents, dispersion media, solvents, solubilizing agents, suspending agents, emulsifying agents, wetting agents, coatings, isotonic agents, sweetening, flavoring and perfuming agents, antibacterial and antifungal agents, absorption delaying agents, and the like. The use of such media and agents for the manufacture of medicaments is well known in the art (see, for example, Remington's Pharmaceutical Sciences, E.W. Martin, 18th Ed., 1990, Mack Publishing Co., Easton, PA).

Examples

The following examples describe some of the preferred modes of making and practicing the present invention. However, it should be understood that these examples are for illustrative purposes only and are not meant to limit the scope of the invention. Furthermore, unless the description in an Example is presented in the past tense, the text, like the rest of the specification, is not intended to suggest that experiments were actually performed or data were actually obtained.

The novel biomimetic approach to the synthesis of rocaglamides, aglains and forbaglins has recently been described, by the Applicants, in a scientific article (B. Gerard *et al.*, J. Am. Chem. Soc., 2004, 126: 13620-13621), which is incorporated herein by reference in its entirety.

General Information

Melting points were recorded on a Mel-Temp (Laboratory Devices). Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. Methylene chloride, acetonitrile, methanol, and benzene were purified by passing through two packed columns of neutral alumina (Glass Contour, Irvine, CA). 3-Hydroxyflavone was purchased from Indofine Chemical Company, Inc. (Hillsborough, NJ).

Nuclear Magnetic Resonance. ^{1}H-NMR spectra were recorded at 400 MHz at ambient temperature with $CDCl_3$ as solvent unless otherwise stated. ^{13}C-NMR spectra were recorded at 75.0 MHz at ambient temperature with $CDCl_3$ as solvent unless otherwise stated. Chemical shifts are reported in parts per million (ppm) relative to $CDCl_3$ (^{1}H, δ 7.24; ^{13}C, δ 77.0) or acetone-d_6 (^{1}H, δ 2.04; ^{13}C, δ 207.6, 30.0). Data for ^{1}H-NMR are reported as follows: chemical shift, integration, multiplicity (abbreviations are as follows: app = apparent, par obsc = partially obscure, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants. All ^{13}C-NMR spectra were recorded with complete proton decoupling.

Infrared Spectroscopy. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. Low and high-resolution mass spectra were obtained at the Boston University Mass Spectrometry Laboratory using a Finnegan MAT-90 spectrometer.

Chromatography. HPLC analyses were carried out on an Agilent 1100 series HPLC (CHIRALCEL OD, Column No. OD00CE-AI015 and Agilent Zorbax SB-C18). Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates; and flash chromatography, using 200-400 mesh silica gel (Scientific Absorbents, Inc.).

Photochemical Irradiation. Photochemical irradiation experiments were performed using a Hanovia 450 W medium pressure mercury lamp housed in a water-cooled quartz immersion well or using an ethylene glycol cooling system (Neslab, RTE-140).

Pyrex test tubes (16 x 100 mm) were mounted on a support approximately 0.5 cm from the immersion well lamp. An uranium filter was obtained from James Glass (Hanover, MA).

All other reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

Example 1: Photochemical Irradiation of 3-Hydroxyflavone

Irradiation of 3-Hydroxyflavone in the Presence of Methyl Cinnamate

To a (16 x 100 mm) test tube was added 3-hydroxyflavone **13** (400 mg, 1.7 mmol) and methyl cinnamate **14** (650 mg, 4 mmol) in 8 mL of anhydrous acetonitrile. After degassing with argon for 5 minutes, the mixture was irradiated (Hanovia UV lamp uranium filter, water used for cooling) at room temperature for 2 hours. The solution was concentrated in *vacuo* to afford a pink-yellow oil.

Purification *via* flash chromatography (60:40 hexanes/EtOAc) yielded 92 mg (0.23 mmol, 15 %) of cyclopenta[*b*]tetrahydrobenzofuran **15** and 370 mg (0.94 mmol, 56 %) of a mixture of cyclopenta[*bc*]benzopyran **16** and benzo[*b*]cyclobutapyran-8-one **17** as colorless solid. Compound **17** was quantitatively converted to cyclopenta[*bc*]benzopyran **16** by thermolysis (EtOAc, 65°C, 4 hours).

***Cyclopenta[b]tetrahydrobenzofuran* 15.** White solid: mp 76-78°C; IR ν_{max} (film): 3449, 3064, 3033, 2955, 2920, 1740, 1697, 1682, 1596, 1476, 1254, 1223, 755 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46-6.97 (14 H, m), 4.48 (1 H, d, J = 13 Hz), 3.96 (1 H, d, J = 13 Hz), 3.59 (3 H, s), 3.01 (1 H, s) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): 208.9, 168.8, 159.6, 136.9, 134.9, 132.1, 129.1, 129.0, 128.9, 128.3,134.9, 132.1, 129.1, 129.0, 128.9, 128.3, 127.9, 126.5, 125.8, 124.8, 122.5, 110.7, 94.0, 87.8, 59.3, 52.4, 52.3 ppm; HRMS (EI) m/z calculated for $C_{25}H_{20}O_5$, 400.1311; found, 401.1429 (M+H).

***Cyclopenta[bc]benzopyran* 16.** White solid: mp 78-81°C; IR ν_{max} (film): 3452, 3060, 3033, 2940, 1767, 1736, 1608, 1584, 1483, 1452, 1210, 905 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.82 (14 H, m), 4.631 (1 H, d, J = 9.2 Hz), 3.645 (1

H, d, $J = 9.2$ Hz), 3.606 (3 H, s), 3.57 (1 H, s) ppm; ^{13}C-NMR(75 MHz, $CDCl_3$) δ 208.4, 170.1, 150.9, 138.2, 133.4, 130.8, 129.8, 128.9, 128.7, 128.4, 128.0, 127.9, 127.5, 127.4, 127.3, 126.8, 126.6, 124.9, 122.1, 116.1, 85.1, 79.8, 57.0, 54.2, 52.8 ppm; HRMS (CI/NH_3) m/z calculated for $C_{25}H_{20}O_5$, 400.1311; found, 401.1357 (M+H).

***Benzo[b]cyclobutapyran-8-one* 17.** White solid: mp 68-70 °C; IR ν_{max} (film): 3448, 2922, 2851, 1743, 1597, 1558, 1475, 1248, 1055, 998, 965, 755 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63-7.61 (2 H, m), 7.25-6.95 (12 H, m), 4.25 (1 H, d, $J = 8.8$ Hz), 3.74 (1 H, d, $J = 8.8$ Hz), 3.55 (3 H, s), 3.27 (1 H, s) ppm; ^{13}C-NMR δ 190.33, 169.6, 151.5, 139.4, 135.4, 130.2, 129.9, 128.9, 128.7, 128.4, 128.1, 127.8, 127.5, 127.4, 126.8, 124.9, 124.6, 121.3, 116.5, 97.5, 88.6, 60.9, 54.3, 52.4 ppm; HRMS (CI/NH_3) m/z calculated for $C_{25}H_{20}O_5$, 400.1311; found, 401.1357 (M+H).

Example 2: Conversion of Cycloadduct 16 to a Forbaglin Ring System

50 mg of cyclopenta[*bc*]benzopyran **16** (0.125 mmol, 1 equiv) were dissolved in a mixture of methanol (30 %) and benzene (0.9 mL / 2.1 mL). $Pb(OAc)_4$ (55 mg, 0.125 mmol, 1 equivalent) was then added portionwise at room temperature and the reaction was stirred for 30 minutes at room temperature. After removal of the solvent *in vacuo*, the resulting residue was diluted with water (5 mL) and EtOAc (5 mL). After separation of the organic layer, the aqueous layer was further extracted twice with EtOAc (5 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (20 % EtOAc in hexane) afforded 46 mg (0.11 mmol, 85 %) of **18:19** as a colorless solid (2:1 mixture of keto/enol tautomers.

***Benzo[b]oxepines* 18/19**. Colorless solid: mp 178-181°C; IR ν_{max} (film): 3060, 3033, 2959, 2924, 1759, 1747, 1684, 1602, 1444, 1434, 1308, 1244; 1102 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64-7.62 (2 H, d, $J = 7.2$ Hz), 7.44-7.28 (8 H, m), 7.18-7.16 (4 H, m), 5.12 (1 H, d, $J = 10$ Hz), 4.41 (1 H, d, $J = 10$ Hz), 3.66 (3 H, s), 3.16 (3 H, s) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 193.2, 156.7, 154.2, 139.0, 134.8, 132.4, 129.2, 129.1, 128.9, 128.7, 128.3, 128.2, 127.8, 127.7, 127.6, 127.4, 126.9,

126.7, 122.3, 121.9, 121.8, 121.6, 64.9, 52.5, 52.2, 52.0, 51.8, 49.8, 46.7 ppm; HRMS (CI/NH_3) m/z calculated for $C_{26}H_{22}O_6$, 430.1416; found, 431.1516 (M+H).

Example 3: Conversion of Cycloadduct 16 to a Dehydrorocaglate Ring System

To a solution of cyclopenta[*bc*]benzopyran **16** (50 mg, 0.125 mmol, 1 equivalent) in MeOH (3 mL) at room temperature was added a solution of NaOMe (17 mg, 0.31 mmol, 2.5 equivalents) in MeOH (1 mL) at room temperature. The resulting solution was stirred for 40 minutes at 65°C. After quenching the reaction with saturated NH_4Cl at room temperature, 10 mL of EtOAc was added. The organic layer was separated and washed with water (2 x 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (20 % EtOAc in hexane) afforded 45 mg (0.11 mmol, 90 %) of the corresponding rocaglates **20/21** as a white solid.

***Cyclopenta[b]tetrahydrobenzofurans* 20/21**. White solid: mp 141-143°C IR ν_{max} (film): 3066, 3027, 2954, 2923, 2856, 1758, 1730, 1650, 1594, 1454, 1279, 1247, 1146, 975 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, 1:1 mixture of keto/enol tautomers **20**:**21**) δ 7.52-6.88 (28 H, m), 5.28 (1 H, s), 4.13 (2 H, dd, J = 13.6 Hz), 3.63 (3 H, s), 3.57 (3 H, s), 2.66 (1 H, s), 2.10 (1 H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 167.1, 159.8, 132.6, 131.1, 128.8, 128.0, 127.8, 127.7, 127.6, 127.6, 127.3, 127.2, 126.9, 126.8, 126.6, 126.2, 125.3, 124.8, 122.6, 121.8, 119.5, 112.4, 110.6, 98.7, 57.4, 56.7, 55.8, 52.9, 51.7 ppm; HRMS (EI) m/z calculated for $C_{25}H_{20}O_5$, 400.1311; found, 401.1427 (M+H).

To a solution of NaH (washed with 3 x 10 mL hexanes, 5 mg, 0.21 mmol, 2.1 equivalents) in THF (2 mL) was added a solution of cyclopenta[*bc*]benzopyran **16** (40 mg, 0.10 mmol, 1 equivalent) in THF (1 mL) at room temperature. The resulting yellow solution was stirred at room temperature for 30 minutes. After addition of thionyl chloride (15 μL, 0.21 mmol, 2.1 equivalents) at room temperature, the mixture was stirred for another hour and then quenched with saturated aqueous $NaHCO_3$. 10 mL of EtOAc were then added and the organic layer was washed with 2 × 3 mL of water and 3 mL brine. The organic extracts were dried over $MgSO_4$, filtered, and

concentrated *in vacuo*. Purification on silica gel (5 % EtOAc in hexane) afforded 21 mg (0.048 mmol, 48 %) of the corresponding 1,3,2-dioxathiolane **22** as a yellow oil.

***1,3,2-Dioxathiolane* 22.** Yellow oil: IR ν_{max} (film): 3025, 2948, 2913, 1716, 1650, 1553, 1243, 1200, 746 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7. 46-7.07 (14 H, m), 3.85 (1 H, s), 3.72 (3 H, s) ppm; ^{13}C-NMR δ 190.4, 165.4, 144.9, 143.1, 132.9, 132.6, 130.8, 130.3, 130.0, 129.6, 129.2, 128.8, 128.7, 128.5, 128.1, 125.6, 124.7, 122.6, 111.1, 52.6, 52.4 ppm; HRMS (EI) m/z calculated for $C_{25}H_{18}O_6S$, 446.0824; found, 447.0805 (M+H).

Example 4: Conversion of Dehydrorocaglate Ring System to Rocaglate Ring System

To a solution of 197 mg (0.75 mmol, 6 equivalents) of $Me_4NBH(OAc)_3$ and 68 μL (1.25 mmol, 10 equivalents) of acetic acid in 3 mL of CH_3CN was added a solution of 50 mg (0.12 mmol, 1 equivalent) of keto rocaglate **20** in 1 mL of CH_3CN. The resulting yellow solution was stirred for 12 hours at room temperature before being quenched with 2 mL of saturated NH_4Cl solution. The solution was then treated with 1 mL of a 3 M aqueous solution of sodium/potassium tartrate and stirred at room temperature for 30 minutes. The aqueous solution was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (20 % EtOAc in hexane) afforded 30 mg (0.047 mmol, 95 %) of **23** as a white solid.

***Cyclopenta[b]tetrahydrobenzofuran* 23.** White solid: mp 176-178°C; IR ν_{max} (film): 3421, 3031, 2925, 1733, 1600, 1476, 1462, 1249, 1102, 976 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41-6.96 (14 H, m), 4.84 (1 H, d, J = 6 Hz), 4.50 (1 H, d, J = 13.6 Hz), 3.99 (1 H, dd, J = 6, 13.6 Hz), 3.66 (3 H, s,), 2.55 (1 H, s), 1.82 (1 H, s), ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.5, 159.1, 136.8, 134.5, 131.4, 127.9, 127.7, 127.6, 127.5, 127.4, 126.8, 126.5, 126.3, 121.6, 111.0, 100.8, 93.3, 79.2, 56.0, 52.2, 50.8 ppm; LRMS (ESI +) m/z calculated for $C_{25}H_{22}O_5$, 402.1467; found, 403.0 (M+H).

Example 5: Photochemical Irradiation of Methoxy-Substituted 3-Hydroxyflavone

Synthesis of Trimethoxy-Substituted 3-Hydroxyflavone

Trimethoxy-substituted 3-hydroxyflavone **24** was synthesized following a procedure adapted from a reaction sequence reported by H. Tanaka and coworkers (Tetrahedron Lett., 2000, 41: 9735-9739). The reaction scheme is presented on Figure 12.

Irradiation of Trimethoxy-Substituted 3-Hydroxyflavone in the Presence of Methyl Cinnamate

To a (16 x 100 mm) test tube was added with kaempferol derivative **24** (200 mg, 0.61 mmol), methyl cinnamate **14** (990 mg, 6.1 mmol), and 20 mL of anhydrous methanol. After degassing with argon, the mixture was irradiated (Hanovia UV lamp, uranium filter) at 0°C for 12 hours under an argon atmosphere. The solution was concentrated in *vacuo* to give a yellow oil. Purification *via* flash chromatography (60:40 hexanes/EtOAc) afforded 100 mg (0.2 mmol, 33 %) of the corresponding trimethoxy cyclopenta[*bc*]benzopyran derivative **25** (mixture of *endo*/*exo* cycloadducts) as a white solid and 50 mg (0.1 mmol, 17 %) of benzo[*b*]cyclo-butapyran-8-one derivative **26** as a yellow solid.

***Trimethoxy Cyclopenta[bc]benzopyran* 25.** White solid: mp 83-85°C. IR ν_{max} (film): 3475, 3013, 2943, 2832, 1786, 1737, 1611, 1590, 1510, 1450, 1255, 1146, 1094, 828 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54-7.52 (2 H, d, J = 8.8 Hz), 7.25-7.23 (2 H, d, J = 8.8 Hz), 7.17-7.49 (2 H, m), 7.10-7.04 (6 H, m), 6.85-6.82 (2 H, m), 6.64-6.60 (4 H, m), 6.19-6.18 (1 H, d, J = 2 Hz), 6.18-6.17 (1 H, d, J = 2 Hz), 6.11-6.10 (1 H, d, J = 2 Hz), 6.08-6.07 (1 H, d, J = 2 Hz), 4.49-4.47 (1 H, d, J = 9.2 Hz), 4.191-4.168 (1 H, d, J = 9.2 Hz), 3.94 (1 H, s), 3.84 (3 H, s), 3.83 (3 H, s), 3.77 (4 H, m), 3.75 (3 H, s), 3.71 (3 H, s), 3.66 (4 H, m), 3.62 (3 H, s), 3.55 (3H, s), 3.29 (1 H, s) ppm; ^{13}C-NMR (70 MHz, $CDCl_3$) δ 205.5, 170.7, 170.6, 161.9, 161.3, 158.8, 158.6, 158.4, 153.6, 152.8, 139.9, 138.1, 130.1, 129.8, 128.9, 128.7, 128.2, 127.8, 127.9, 127.0, 126.5, 125.6, 113.6, 112.7, 112.6, 107.7, 106.5, 97.9, 95.5, 94.4, 94.3, 93.6, 93.4, 92.7, 88.7, 83.6, 81.04, 80.7, 62.4, 57.6, 56.1, 55.9, 55.4, 55.3, 55.1, 54.5, 53.4,

52.2, 51.8 ppm; HRMS (CI/NH_3) m/z calculated for $C_{28}H_{26}O_8$, 490.1628; found, 491.1739 (M+H).

***Trimethoxy benzo[b]cyclobutapyran-8-one* 26.** Yellow solid: mp 79-81°C. IR ν_{max} (film): 3489, 3006, 2948, 2839, 1734, 1729, 1618, 1590, 1516, 1461, 1437, 1299, 1200, 1148, 1096, 909 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53 (2 H, d, J = 8.8 Hz), 7.16 (2 H, m), 7.01 (3 H, m), 6.64 (2 H, d, J = 8.8 Hz), 6.19 (1 H, d, J = 2 Hz), 6.08 (1 H, d, J = 2 Hz), 4.27 (1 H, s), 4.17 (1 H, d, J = 9.6 Hz), 3.84 (4 H, m), 3.75 (3 H, s), 3.67 (3 H, s), 3.56 (3 H, s) ppm.

Example 6: Conversion of Aglains 25 and 26 to a Keto Rocaglate Ring System

Conversion of Aglain 25

To a solution of aglain **25** (60 mg, 0.12 mmol, 1 equivalent) in MeOH (4 mL) was added a solution of NaOMe (13.2 mg, 0.24 mmol, 2.5 equivalents) in MeOH (1 mL) at room temperature. The resulting solution was stirred for 40 minutes at 65°C. After quenching the reaction with saturated NH_4Cl, 10 mL of EtOAc was then added, and the organic layer was washed with water (2 x 5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford 57 mg (0.12 mmol, 95 %) of crude ketol shift product **27/27'/27"** as a yellow oil which was used without further purification (3:1 mixture of *endo*:*exo* isomers **27'/ 27"** and **27,** see chemical structures of **27, 27', 27"** on Figure 13).

***Trimethoxy rocaglate* 27/27'/27".** Yellow oil: IR ν_{max} (film): 3501, 3006, 2947, 2926, 2839, 1762, 1734, 1615, 1513, 1450, 1440, 1255, 1213, 1146, 1033, 1076 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, 1:1 mixture of keto/enol tautomers **27' : 27"**) δ 7.34-7.32 (2 H, d, J = 6.8 Hz), 7.20-7.19 (2 H, m), 7.09-6.86 (15 H, m), 6.65 (2 H, d, J = 8.8 Hz), 6.51 (2 H., d, J = 6.8 Hz), 6.33 (1 H, d, J = 1.6 Hz), 6.17 (1 H, d, J = 1.6 Hz), 6.13 (1 H, d, J = 1.6 Hz), 6.12 (1 H, d, J = 1.6 Hz), 6.05 (1 H, d, J = 1.6 Hz), 6.00 (1 H, d, J = 1.6 Hz), 4.46 (1 H, s), 4.42 (1 H, d, J = 14.8 Hz), 4.36 (1 H, d, J = 14.8 Hz), 4.22 (1 H, d, J = 13.6 Hz), 4.04 (1 H, d, 13.6 Hz), 3.84 (3 H, s), 3.08-3.79 (9 H, m), 3.77 (9 H, m), 3.70 (6 H, m), 3.64 (6 H, m), 3.57 (3 H, s), 3.30 (1 H, s), 3.01 (1

H, s) ppm; HRMS (EI) m/z calculated for $C_{28}H_{26}O_8$, 490.1628; found, 490.9634 (M+H).

Conversion of Aglain 26

Benzo[*b*]cyclobutapyran-8-one **26** was subjected to the aforementioned conditions using 20 mg (0.041 mmol, 1 equivalent) of **26** in MeOH (2 mL) and NaOMe (5 mg, 0.09 mmol, 2.5 equivalents) in MeOH (1 mL). 18 mg of crude ketol shift product **27** (0.036, 90 %) was isolated and used without further purification (only the *endo* isomer was isolated).

Example 7: Hydroxyl-Directed Reduction of Keto Rocaglate 27

Hydroxyl-Directed Reduction of Trimethoxy Keto Rocaglate 27

To a solution of 184 mg (0.70 mmol, 6 equivalents) of $Me_4NBH(OAc)_3$ and 63 μL (1.16 mmol, 10 equivalents) of acetic acid in 3 mL of CH_3CN was added a solution of 57 mg (0.12 mmol, 1 equivalent) of **27** in 1 mL of CH_3CN. The resulting yellow solution was stirred for 12 hours at room temperature before being quenched with 2 mL of saturated NH_4Cl. The solution was then treated with 1 mL of a 3 M aqueous solution of sodium/potassium tartrate and stirred at room temperature for 30 minutes. The aqueous solution was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification on silica gel (40 % EtOAc in hexane) afforded 30 mg (0.030 mmol, 51 %) of the corresponding *endo* methyl rocaglate **28** and 18 mg (0.017 mmol, 27 %) of the corresponding *exo* methyl rocaglate **29**.

***Endo Methyl Rocaglate* 28.** White solid: mp 92-93°C; R ν_{max} (film): 3013, 2954, 2926, 2853, 1734, 1615, 1517, 1457, 1433, 1262, 1195, 1150, 1031, 832 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.09 (2 H, d, J = 9.2 Hz), 7.05-7.03 (3 H, m), 6.84 (2 H, m), 6.65 (2 H, d, *J* = 9.2 Hz), 6.27 (1 H, d, *J* = 2 Hz), 6.1 (1 H, d, *J* = 2 Hz), 5.01 (1 H, dd, *J* = 6.4, 1.2 Hz), 4.28 (1 H, d, *J* = 14.4 Hz), 3.80 (1 H, dd, *J* = 14.4, 6.4 Hz), 3.86 (3 H, s), 3.82 (3 H, s), 3.69 (3 H, s), 3.63 (3 H, s), 3.50 (1 H, s), 1.81 (1 H, br) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.5, 164.1, 160.9, 158.8, 157.0, 137.0, 129.0, 128.4, 127.8, 127.7, 126.5, 112.7, 107.7, 101.9, 93.7, 92.7, 89.5, 79.6, 60.4, 55.8,

55.1, 55.0, 51.9, 50.6 ppm; δ HRMS (CI/NH_3) m/z calculated for $C_{28}H_{28}O_8$, 492.1784; found, 493.1891 (M+H).

***Exo Methyl Rocaglate* 29.** Foamy yellow: solid mp 84-85°C. IR ν_{max} (film): 3031, 3006, 2958, 2936, 2846, 1730, 1636, 1430, 1307, 1258, 1132, 103 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 (2 H, d, J = 8.8 Hz), 7.17-1.15 (3 H, m), 6.95-6.94 (2 H, m), 6.87 (2 H, d, J = 8.8 Hz), 6.12 (1 H, d, J = 1.6 Hz), 6.06 (1 H, d, J = 1.6 Hz), 4.76 (1 H, dd, J = 10.2, 1.6 Hz), 4.02 (1 H, d, J = 12.8 Hz), 3.82 (3 H, s), 3.78 (3 H, s), 3.77 (3 H, s), 3.60 (3 H, s), 3.23 (1 H, dd, J = 12.8, 10.2 Hz), 1.81 (1 H, s) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.1, 164.1, 162.0, 159.4, 157.9, 135.0, 129.1, 128.4, 128.0, 127.3, 119.7, 113.6, 105.1, 99.5, 92.6, 91.4, 88.8, 83.9, 55.8, 55.8, 55.4, 54.8, 52.3, 50.9 ppm; HRMS (CI/NH_3) m/z calculated for $C_{28}H_{28}O_8$, 492.1784; found, 493.1891 (M+H).

The crude ketol shift product **27** obtained from benzo[*b*]cyclobutapyran-8-one derivative **26** was subjected to the aforementioned conditions using 58 mg of $Me_4NBH(OAc)_3$ (0.22 mmol, 6 equivalents), 20 μL (0.37 mmol, 10 equivalents) in 3 mL of MeCN, and 18 mg (0.037 mmol, 1 equivalent) of compound **26**. 13 mg of *endo* methyl rocaglate **28** (0.021 mmol, 75 %) was obtained.

Tables 1, 2, and 3 shown below summarize data comparison of natural (F. Ishibashi *et al.*, Phytochemistry, 1993, 32: 307-310) and synthetic *endo* methyl rocaglate **28**.

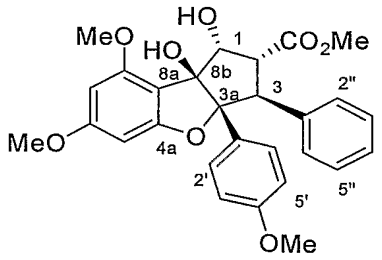


Table 1. ^{1}H-NMR Data (400 MHz, $CDCl_3$) for natural and synthetic *endo* methyl rocaglate **28**.

Position	^{1}H-NMR (400 Hz in $CDCl_3$)	
	Natural	Synthetic 28
1	5.02 (dd, 1.6, 6.8)	5.01 (dd, 1.2, 6.4)
2β	3.91 (dd, 6.8, 14.4)	3.91(dd, 6.4, 14.4)
3α	4.32 (d, 14.4)	4.27 (d, 14.4)
5	6.29 (d, 2.4)	6.26 (d, 2)
7	6.13 (d, 2.4)	6.10 (d, 2)
2', 6'	7.11 (d, 8.8)	7.10 (d, 9.2)
3', 5'	6.68 (d, 8.8)	6.65 (d, 9.2)
2", 6"	6.88 (m)	6.85 (m)
3", 4", 5"	7.07 (m)	7.04 (m)
OMe-6	3.88 (s)	3.86 (s)
OMe-8	3.84 (s)	3.81 (s)
OMe-4'	3.71 (s)	3.67 (s)
CO_2Me	3.65 (s)	3.62 (s)
OH	1.78, 3.60 (br, s)	1.88, 3.50 (br, s)

Table 2. ^{13}C-NMR Data (75 MHz, acetone-d_6) for natural and synthetic *endo* methyl rocaglate **28**.

Position	^{13}C NMR (75 Hz) in acetone d_6	
	Natural	Synthetic 28
1	80.6	80.3
2	51.5	51.1
3	55.8	55.5
3a	102.6	102.2
5	89.8	89.4
7	92.8	92.3
8a	112.8	112.4
8b	94.2	94.1
1'	128.9	128.4
2', 6'	129.9	129.6
3', 5'	112.8	112.4
1"	139.2	138.8
2", 6"	128.2	128.4
3", 5"	128.8	128.4
4"	126.8	126.4
4a, 6, 8, 4'	158.6, 159.3, 161.7, 164.6	158.3, 158.9, 161.4, 164.3
ArOMe	55.2, 55.9, 56.0	54.8, 55.3, 55.5
C=O	170.7	170.4
CO_2Me	51.5	51.1

Table 3. Miscellaneous data for natural and synthetic *endo* methyl rocaglate **28**

	Natural methyl rocaglate	**Synthetic methyl rocaglate 28**
Mp	88-91	92-93
HRMS (EI), *m/z* (rel. int.)	492.1797 $[M]^+$ 492 (3), 390 (6), 313 (46), 300 (100), 285 (59), 181 (66), 135 (78), 131 (50), 103 (55).	492.1814 $[M]^+$ 492 (2), 390 (5), 313 (40), 300 (100), 285 (23), 181 (21), 135 (16), 131 (24),
IR ν_{max} cm^{-1} (KBr)	3489, 1750, 1623, 1611, 1513, 1247, 1218, 1200, 1149, 1118	3486, 1734, 1615, 1517, 1251, 1212, 1195, 1150, 1115.

Tables 4 and 5 shown below summarize data comparison of compound **29** and *exo* methyl rocaglate synthesized by Kraus and Sy (G.A. Kraus and J.O. Sy, J. Org. Chem., 1989, 54: 77-83).

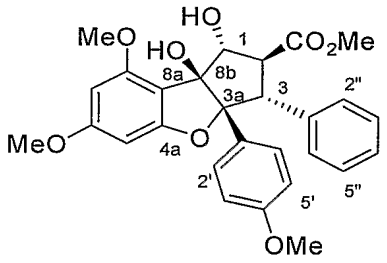


Table 4. ^{1}H-NMR Data (400 MHz, $CDCl_3$) for Kraus' *exo* methyl rocaglate and compound **29**.

Position	**^{1}H NMR (400 Hz) in $CDCl_3$**	
	***Exo* methyl rocaglate**	**29**
1	4.77 (d, 11)	4.76 (dd, 1.6, 10.2)
2α	3.24 (dd, 11, 13)	3.23 (dd, 10.2, 12.8)
3β	4.03 (d, 13)	4.02(d, 12.8)
5	6.12 (d, 2)	6.12 (d, 1.6)
7	6.05 (d, 2)	6.06 (d, 1.6)
2', 6'	7.33 (d, 8)	7.34 (d, 8.8)
3', 5'	6.87 (d, 8)	6.87 (d, 8.8)
2", 6"	6.94 (m)	6.95 (m)
3", 4", 5"	7.16 (m)	7.16 (m)
Ar-OMe	3.81, 3.78, 3.76	3.82, 3.78, 3.77
CO_2Me	3.60	3.60

Table 5. ^{13}C-NMR Data (75 MHz, $CDCl_3$)for Kraus'*exo* methyl rocaglate and compound **29**.

Position	^{13}C NMR (75 MHz) in $CDCl_3$	
	Exo methyl rocaglate	Compound 29
1	83.8	83.9
2	50.8	50.90
3	55.7	55.9
3a	91.2	91.4
5	88.7	88.7
7	92.5	92.6
8a	105.0	105.1
8b	99.3	99.5
1'	129.0	129.1
2', 6'	missing	119.6
3', 5'	113.5	113.6
1"	134.8	134.9
2", 6"	128.3	128.4
3", 5"	127.8	127.9
4"	127.1	127.3
4a, 6, 8, 4'	163.9, 161.9, 159.2, 156.8	164.1, 162.0, 159.4, 157.9
ArOMe	55.7, 55.3, 54.7	55.8, 55.4, 54.8
C=O	172.95	173.1
CO_2Me	52.1	52.3

Example 8: Reduction of Cyclopenta[*bc*]benzopyran 16

To a solution of cyclopenta[*bc*]benzopyran **16** (100 mg, 0.25 mmol, 1 equivalent) in 10 mL of MeOH was added sodium borohydride (15 mg, 0.375 mmol, 1.5 equivalent) portionwise over 5 minutes at 0°C. The resulting solution was warmed to room temperature and stirred for 4 hours. The reaction was then quenched with saturated NH_4Cl, and diluted with EtOAc (10 mL) and water (10 mL). After separation of the organic layer, the aqueous layer was extracted twice with EtOAc (5 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

The resulting diol (75 mg, 0.18 mmol, 1 equivalent) was directly subjected to acylation using 4-bromobenzoyl chloride (94 mg, 0.43 mmol, 1.2 equivalent) and DMAP (44 mg, 0.36 mmol, 2 equivalents) in 3 mL of CH_2Cl_2. The reaction was

stirred at room temperature for 24 hours. The reaction mixture was diluted using CH_2Cl_2 (5 mL) and washed with water (2 x 5 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (30 % EtOAc in hexane) provided 95 mg (0.16 mmol, 85 %) of 4-bromobenzoate **30** as a colorless solid.

***4-Bromobenzoate* 30.** Colorless solid: mp 73-74 (benzene); IR ν_{max} (film): 3468, 3065, 3032, 2952, 2926, 2854, 1725, 1612, 1590, 1484, 1458, 1269, 911, 754; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46-7.43 (2 H. d, J = 10.2 Hz), 7.28-7.19 (6 H, m), 7.00-6.90 (10 H, m), 6.47 (1 H, s), 4.20-4.18 (1 H, s, 8.4 Hz), 3.80 (1 H, s), 3.63-3.61 (1 H, d, J = 8.4 Hz), 3.48 (3 H, s) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.4, 166.2, 152.0, 139.2, 136.4, 131.7, 131.5, 129.9, 129.2, 128.8, 128.2, 127.9, 127.8, 127.7, 126.9, 126.5, 124.8, 123.6, 120.9, 115.7, 87.8, 77.8, 73.8, 60.5, 55.3, 52.4 ppm; HRMS (CI/NH_3) m/z calculated for $C_{32}H_{25}BrO_6$, 584.0835; found, 585.0931(M+H).

The X-ray crystal structure of compound **30** is presented on Figure 20.

Crystals of compound **30** suitable for X-ray analysis were obtained by slow evaporation from benzene. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 248425). Copies of the data can be obtained free of charge on application to the CCDC, (12 Union Road, Cambridge CB21EZ, UK; Fax: (+44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Crystal data and structure refinement for compound **30** are presented in Table 6.

Table 6. Crystal data and structure refinement for compound **30**.

Identification code	Compound **30**	
Empirical formula	C50 H43 Br O6	
Formula weight	819.75	
Temperature	213(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 12.027(2) Å	α= 90°.
	b = 27.228(5) Å	β= 95.966(4)°
	c = 12.927(2) Å	γ = 90°
Volume	4210.2(13) $Å^3$	
Z	4	
Density (calculated)	1.293 Mg/m^3	
Absorption coefficient	1.026 mm^{-1}	
F(000)	1704	
Crystal size	0.10 x 0.08 x 0.08 mm^3	
Theta range for data collection	1.70 to 25.00°.	
Index ranges	-14<=h<=14, -32<=k<=26, -12<=l<=15	
Reflections collected	22422	
Independent reflections	7405 [R(int) = 0.1260]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7405 / 0 / 516	
Goodness-of-fit on F^2	0.998	
Final R indices [I>2sigma(I)]	R1 = 0.0655, wR2 = 0.1101	
R indices (all data)	R1 = 0.2038, wR2 = 0.1455	
Largest diff. peak and hole	0.504 and -0.513 e.$Å^{-3}$	

Example 9: Reactivity of Cyclopenta[*bc*]benzopyran 15

To a solution of lithium aluminium hydride (26 mg, 0.89 mmol, 3 equivalents) in THF (5 mL) at 0°C was added a solution of cyclopenta[*b*]tetrahydrobenzofuran **15** (90 mg, 0.225 mmol, 1 equivalent) in 2 mL of THF. The resulting solution was warmed to room temperature and stirred for 3 hours. The reaction was then cooled at 0°C and quenched with 1 mL of water followed by 1 mL of 1 N aqueous NaOH. The

resulting solution was filtered and the filtrate was evaporated *in vacuo* to afford the crude triol (63 mg, 0.17 mmol, 75 %).

The crude triol was then directly subjected to acylation with 4-bromobenzoyl chloride (82 mg, 0.34 mmol, 2.2 equivalents) and DMAP (63 mg, 0.51 mmol, 3 equivalents) in 5 mL of CH_2Cl_2. The reaction was then stirred for 24 hours at room temperature. The mixture was diluted using CH_2Cl_2 (5 mL) and washed with water (2 x 5 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (30 % EtOAc in hexane) afforded 100 mg (0.14 mmol, 80 %) of *bis*-4-bromobenzoate **31** as a colorless solid,

***Bis-4-bromobenzoate* 31.** Colorless solid: mp 256-257°C (petroleum ether / chloroform); IR ν_{max} (film): 3420, 3035, 2956, 2870, 1717, 1701, 1590, 1475, 1465, 1398, 1365, 1271, 1216, 1125 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.70-7.68 (2 H, d, J = 8.4 Hz), 7.59-7.56 (2 H, d, J = 8.4 Hz), 7.51-7.48 (2 H, d, J = 8.4 Hz),7.40-7.18 (14 H, m), 6.98-6.59 (2 H, d, J = 8.4 Hz), 5.93 (1 H, d, J = 11.2 Hz), 4.53 (1 H, dd, J = 11.2, 8.4 Hz), 4.33 (1 H, dd, J = 11.2, 5.6 Hz), 3.53 (1 H, m), 3.19 (1 H, dd, J = 12.4, 11.6 Hz), 2.98 (3 H, s) 2.01 (1 H, s) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.2, 165.4, 159.6, 137.5, 137.0, 131.8, 131.3, 131.2, 131.0, 129.0, 128.7, 128.4, 128.2, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 126.7, 126.5, 121.5, 110.1, 97.5, 89.3, 86.8, 62.9, 50.4, 48.4, 29.6 ppm; δ HRMS (CI/NH_3) m/z calculated for $C_{38}H_{28}Br_2O_6$, 738.0253; found, 739.0217 (M+H).

The X-ray crystal structure of compound **31** is presented on Figure 21. Crystals of compound **31** suitable for X-ray analysis were obtained by slow evaporation from benzene. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 248425).

Crystal data and structure refinement for compound **31** are presented in Table 7.

Table 7. Crystal data and structure refinement for compound **31**.

Identification code	Compound **31**	
Empirical formula	C38 H28 Br2 O6	
Formula weight	740.42	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 25.4111(10) Å	α= 90°.
	b = 16.5031(6) Å	β= 106.677O(10)°°
	c = 16.4599(6) Å	γ = 90°
Volume	6612.3(4) $Å^3$	
Z	8	
Density (calculated)	1.488 Mg/m^3	
Absorption coefficient	2.498 mm^{-1}	
F(000)	2992	
Crystal size	0.40 x 0.15 x 0.03 mm^3	
Theta range for data collection	0.84 to 20.81°	
Index ranges	-25<=h<=25, -13<=k<=16, -14<=l<=16	
Reflections collected	23839	
Independent reflections	6644 [R(int) = 0.0507]	
Completeness to theta = 25.00°	95.9 %	
Absorption correction	None	
Refinement method	Semiempirical by SADABS	
Data / restraints / parameters	6644 / 0 / 829	
Goodness-of-fit on F^2	1.022	
Final R indices [I>2sigma(I)]	R1 = 0.0940, wR2 = 0.1169	
R indices (all data)	R1 = 0.2038, wR2 = 0.1455	
Largest diff. peak and hole	0.385 and -0.467 $e.Å^{-3}$	